*Development of Thermally Stable Versions of the Burgess Reagent. Approaches to the Chemoenzymatic Total Synthesis of Morphine*

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Submitted in partial fulfillment
of the requirements for the degree of

*Master of Science*

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**Abstract**

The present studies describe our recent work on expanding the use of the Burgess reagent and its reaction with oxiranes. Several new variants of the Burgess reagent and its chiral auxiliary version were evaluated for their thermal stability by NMR spectroscopy. Three new versions of the reagent were synthesized and their stability was determined. The reactivity of all five Burgess reagents was compared in a dehydration reaction and reactions with epoxides and diols.

Progress toward a chemoenzymatic synthesis of morphine is also included in this report. The synthesis began with the whole cell oxidation of bromobenzene by *Escherichia coli* JM109(pDTG601). The preparation of several precursors for a key step involving the Johnson-Claisen rearrangement and progress toward the total synthesis are described.

**Acknowledgements**

There are many people to whom I am very indebted to for all of their help and support. First, I would like to thank my advisor, Dr. Tomas Hudlicky for allowing me the opportunity to work with him and for all of his patience and unwavering interest in my progress and development as a chemist.

I would like to thank the members of my graduate committee Dr. Georgi Nikonov, Dr. Tony Yan, Dr. Tomas Hudlicky, Dr. Heather Gordon, and the external examiner Dr. James Green of the University of Windsor. Thanks are also due to Dr. Stuart Rothstein, Chris Skorski and Beulah Alexander for making sure I had all of the necessary paperwork turned in and helping me navigate the administrative bureaucracy.

Razvan Simionescu and Tim Jones are greatly appreciated for their help in both acquiring and interpreting NMR and mass spectra. Thanks are due to Gary McDonnell at the Electronics Shop, Steve Crumb at the Machine Shop and John and Jordan Vandenhoff at the Glass Shop for keeping our lab running smoothly.

I have had the opportunity to work with many talented chemists in my time at Brock University. Dr. Robert Carroll, Dr. Mohammed Haque, Dr. Hannes Leisch, Elisabeth Kloser, Dr. Bradford Sullivan, Dr. Jon Collins, Dr. Ales Machara, Dr. Lukas Werner, Mrs. Martina Wernerova, Dr. Jan Duchek, Amy English, Melissa Drouin, Jacqueline Gilmet, Vigi George, Ignacio Carrera, Leon Sun, Tyler Bissett, Robert Giacometti, David Ilceski, David Adams, Sergey Vshyvenko, Graeme Piercey, Vimal Varghese, Christian Aichinger, Vladislav Semak, Yasmeen Albalawi, Hollich Ho and Jon

Scattalon. Thanks are also due to Brock University and the National Science and Engineering Research Council of Canada (NSERC) for funding my studies.

Finally, I am grateful to my parents, my brother Benjamin, my sisters Lynn and Anna and the rest of my family.

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**List of Abbreviations**

| | |
|---|---|
| 2,4 DNP | 2,4-dinitrophenyl hydrazine |
| Ac | acetyl |
| Boc | *tert*-butyloxycarbonyl |
| $(Boc)_2O$ | di-*tert*-butyl dicarbonate |
| Cbz | carboxybenzyl |
| $CDCl_3$ | deutero-chloroform |
| $CDCl_3$ | chloroform |
| conc. | concentrated |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DAST | diethylaminosulfur trifluoride |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DCE | 1,2 dichloroethane |
| DCM | dichloromethane |
| DEAD | diethyl azodicarboxylate |
| DIAD | diisopropyl azodicarboxylate |
| DIPEA | diisopropylethylamine |
| DMAP | dimethylamino pyridine |
| DME | dimethoxyethane |
| DMF | N,N-dimethylformamide |
| DMSO | dimethyl sulfoxide |

| | |
|---|---|
| dppf | 1,1'-*bis*-(diphenylphosphino)ferrocene |
| dr | diastereomeric ratio |
| EDG | electron donating group |
| EI | electron ionization |
| eq. | equivalent(s) |
| er | enantiomeric ratio |
| $Et_2O$ | diethyl ether |
| $Et_3N$ | triethylamine |
| EtOAc | ethyl acetate |
| EWG | electron withdrawing group |
| FAB | fast atom bombardment |
| h | hour(s) |
| HATU | 2-(1H-7-azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium |
| HCl | hydrochloric acid |
| HMBC | heteronuclear multiple bond correlation |
| Hz | Hertz |
| IBX | 2-iodoxybenzoic acid |
| *i*-Pr | isopropyl |
| IPTG | β-isopropylthiogalactopyranoside |
| IR | infrared spectroscopy |
| *J* | coupling constant |
| LAH | lithium aluminum hydride |

| | |
|---|---|
| LDA | lithium diisopropyl amide |
| M* | menthyl |
| MeCN | acetonitrile |
| min | minute(s) |
| mp | melting point |
| MS | mass spectroscopy |
| *n*-BuLi | *n*-butyl lithium |
| NADH | Nicotinamide adenine dinucleotide |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NBA | N-bromoacetamide |
| NMR | nuclear magnetic resonance |
| *p*-Tol | *p*-tolyl |
| PAD | potassium azodicarboxylate |
| $PBu_3$ | tributyl phosphine |
| PEG | poly(ethylene glycol) |
| PhH | benzene |
| PhMe | toluene |
| PMB | *p*-methoxybenzyl |
| PMP | *p*-methoxyphenyl |
| $PPh_3$ | triphenyl phosphine |
| ppm | parts per million |
| quant. | quantitative |
| rt | room temperature |

| | |
|---|---|
| TBAF | tetrabutylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| TDS | thexyldimethylsilyl |
| *t*-Bu | *tert*-butyl |
| TDO | toluene dioxygenase |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIBAL | tri-isobutyl aluminum |
| TLC | thin layer chromatography |
| TMS | tetramethylsilane |
| W | Watt(s) |

## 1. Introduction

This thesis is presented in two parts. In the first part, the design of new variants of type **2** of the Burgess reagent **1** and their thermal stability is to be investigated. The second part is concerned with progress toward the total synthesis of morphine **3** with the key steps being biooxidation of bromobenzene **4** and a Claisen rearrangement to set the C-13 quaternary center.

The Burgess reagent **1** is a useful tool for performing a variety of transformations in organic synthesis. However, it is unstable at high temperatures and in the presence of acids. We investigate new variants of the reagent to overcome this instability and then evaluate the stability and reactivity by NMR techniques. The methoxy portion of the carbamate will be replaced with the more electron withdrawing 2,2,2-trifluoroethanol to better stabilize the negative charge. The triethylamine portion will be replaced with the more electron donating *N*-methylpiperidine to stabilize the positive charge (Figure 1).

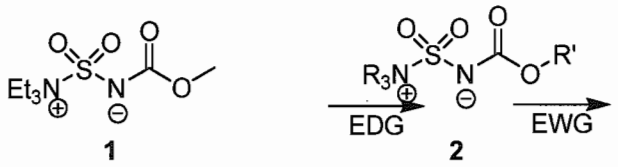



**Figure 1**-Design of new Burgess reagents

Morphine (**3**) is a commonly used analgesic with a complex structure. Its use by mankind has spanned centuries. Our proposed synthetic route, shown in Figure 2, begins with the dihydroxylation of bromobenzene (**13**) with *Escherichia coli* JM109 (pDTG601). Reduction of the distal double bond and coupling with Boc glycine will provide **11** which will be subjected to a Kazmaier-Claisen rearrangement. Subsequent methylation and separation of the diastereomers will give the C-ring fragment **9** which is to be coupled to A-ring fragment **8**. The coupled intermediate will be further elaborated

to the substrate for the second Claisen rearrangement **6**. Subsequent closure of the B- and D-rings and further elaboration should provide morphine (Figure 2).

Connected to the biooxidation of bromobenzene (**13**) to diol **12** was the investigation of several halogen substituted benzoate esters that were tested as substrates for the enzyme toluene dioxygenase (TDO). The yields and physical and spectral properties of the new metabolites will be presented.

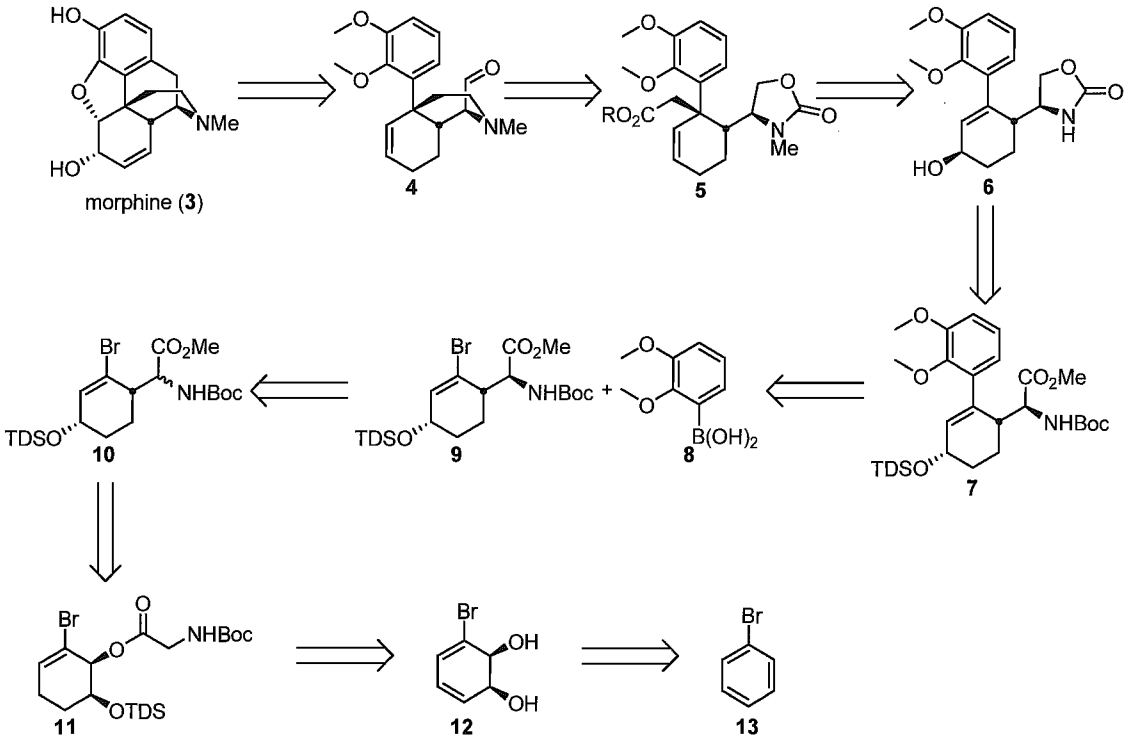


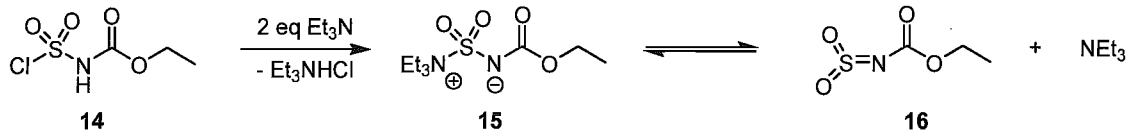

**Figure 2**-Retrosynthetic analysis for morphine

## 2. Historical

### 2.1 Burgess reagent

#### 2.1.1 Development of Burgess reagent and dehydration reactions

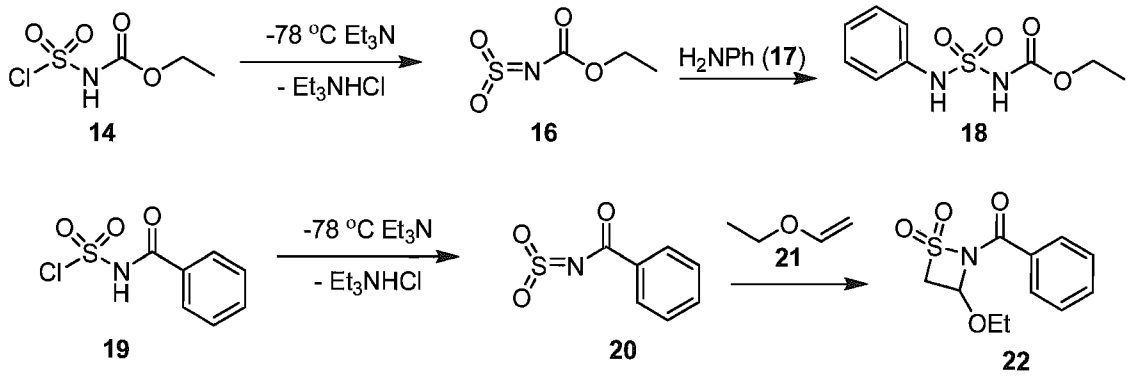
The first reported synthesis of an alkyl *N*-(triethylammoniumsulfonyl)carbamate inner salt was in 1968 when Edward Burgess and George Atkins studied the reactivity of *N*-sulfonylamines.[1] Inner salt **15** was an intermediate that was subjected to fragmentation to prepare *N*-sulfonylamine **16** (Figure 3).




14 15 16

**Figure 3**-Burgess' sulfonylamine preparation

In their previous work **16** was generated *in-situ* by treating **14** with one equivalent of triethylamine and intercepting the unstable sulfonylamine with a nucleophile such as aniline (**17**).[1] The more reactive benzoyl sulfonylamine **19** was also generated in the presence of ethyl-vinyl ether (**21**) to form cycloadduct **22** (Figure 4).




14 16 18

19 20 22

**Figure 4**-Generation of *N*-sulfonylamines[1]

Burgess and Atkins reported several electrophilic additions to **15** (Figure 5).[2] The reaction of **15** with aniline gave **17** in 92 % yield. The addition of *N*-vinylpyrrolidinone

(**23**) to **15** gave **24** in 50 % yield and the addition of isopropanol to **15** gave **26** in low yield.

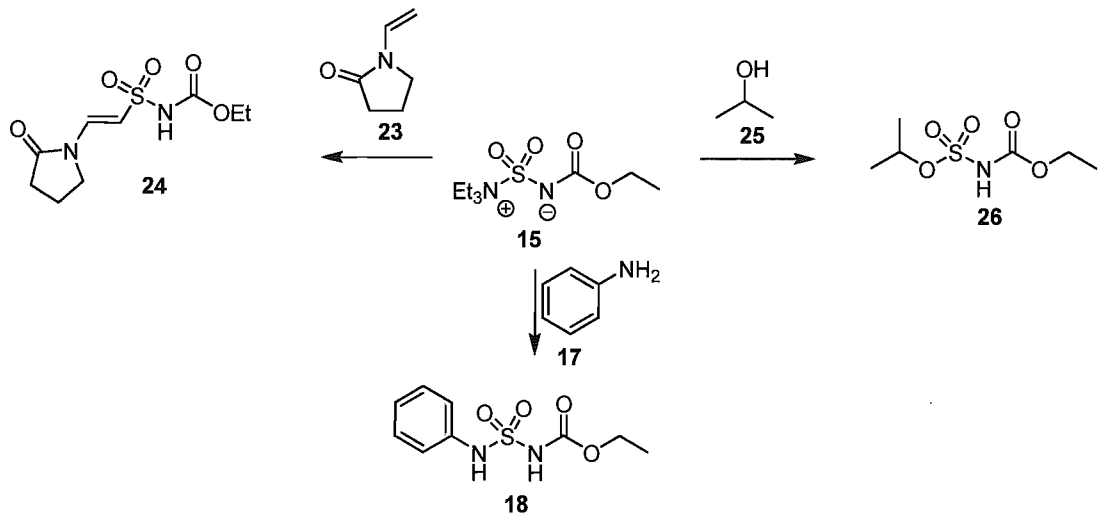



**Figure 5**-Electrophilic addition to *N*-(triethylammoniumsulfonyl)carbamate inner salt[2]

In 1970, Burgess prepared the methyl variant of the inner salt **1**, which would later be named the Burgess reagent. This compound was found to be a very mild dehydrating agent for secondary and tertiary alcohols (Figure 6).[3]

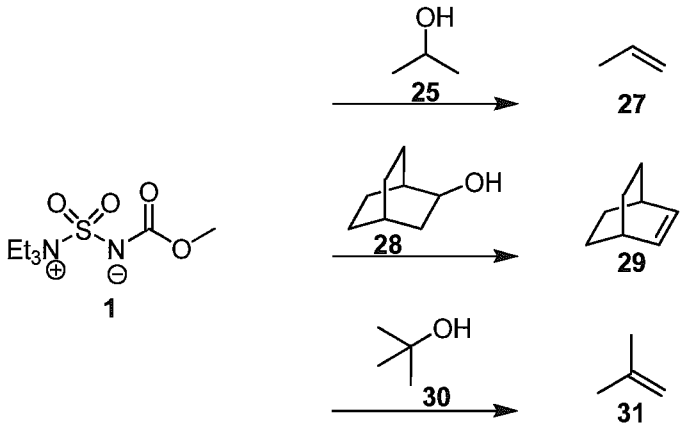



**Figure 6**-Dehydration reactions of secondary and tertiary alcohols with Burgess reagent[3]

When primary alcohols were treated with the Burgess reagent, dehydration did not occur. Instead, primary urethane **32** was formed via an $S_N2$ pathway (Figure 7).[3]

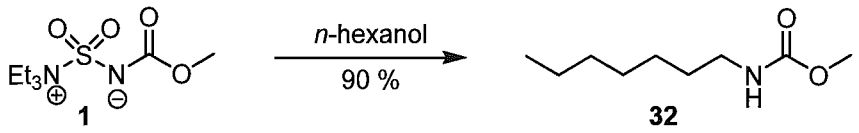



**Figure 7**-Reaction of Burgess reagent with *n*-hexanol[3]

Depending on reaction conditions, allylic alcohols were shown to either undergo dehydration reactions or form urethanes via an $S_N2$ pathway rearrangement (Figure 8).[3]

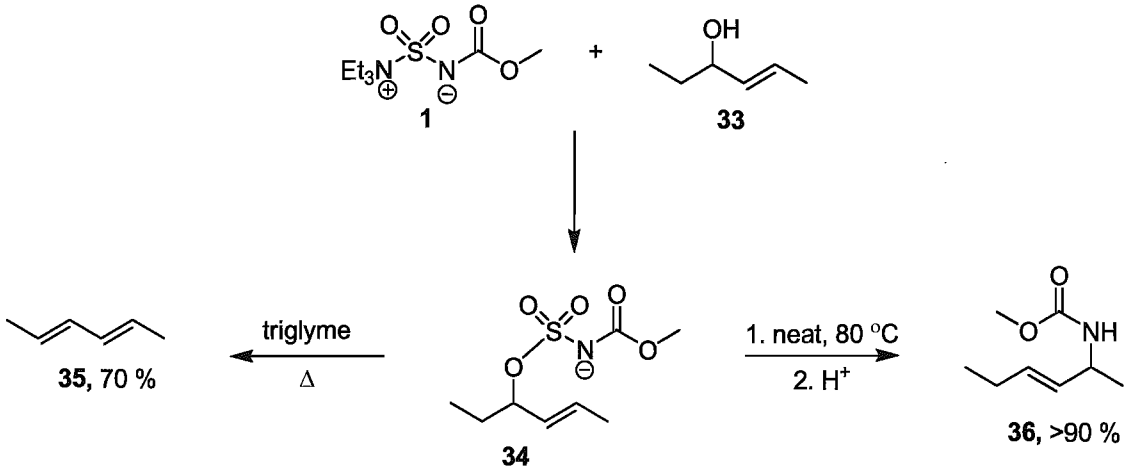



**Figure 8**-Formation of diene or urethane from an allylic alcohol with Burgess reagent[3]

In the 1970 full paper, isotope studies were presented that showed that the elimination of an alcohol by **1** was a *syn*-elimination.[3] *Erythro* and *threo*-2 deutero-1,2-diphenyl ethanol (**37** and **38** respectively) were treated with Burgess reagent. The former yielded only *trans*-stilbene (**39**) while the latter yielded only protio-*trans*-stilbene (**40**). The rate limiting step was shown to be the formation of an ion pair **42** followed by a fast *cis*-β-proton transfer (Figure 9).

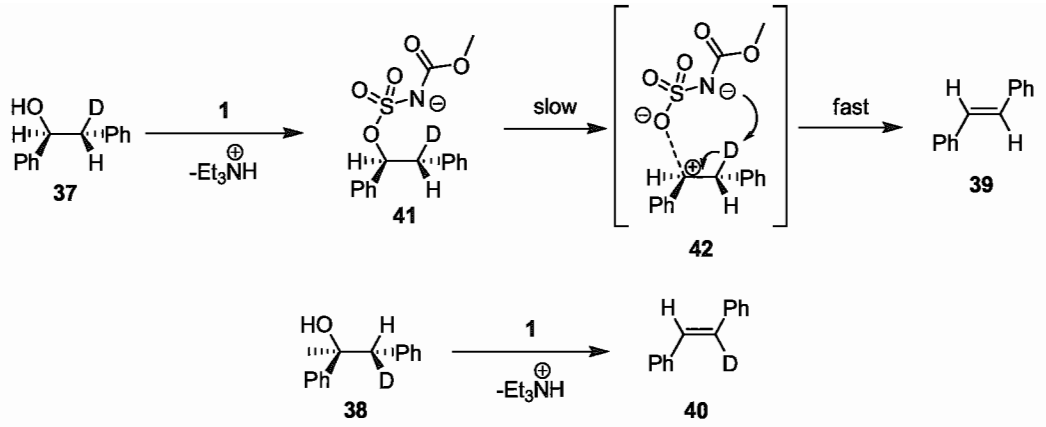



**Figure 9**-Mechanism of dehydration by the Burgess reagent

When the carbocation intermediate in a dehydration reaction is highly stabilized, rearrangements can occur thus making olefin formation less predictable, as in the case of **46** (Figure 10).[3]

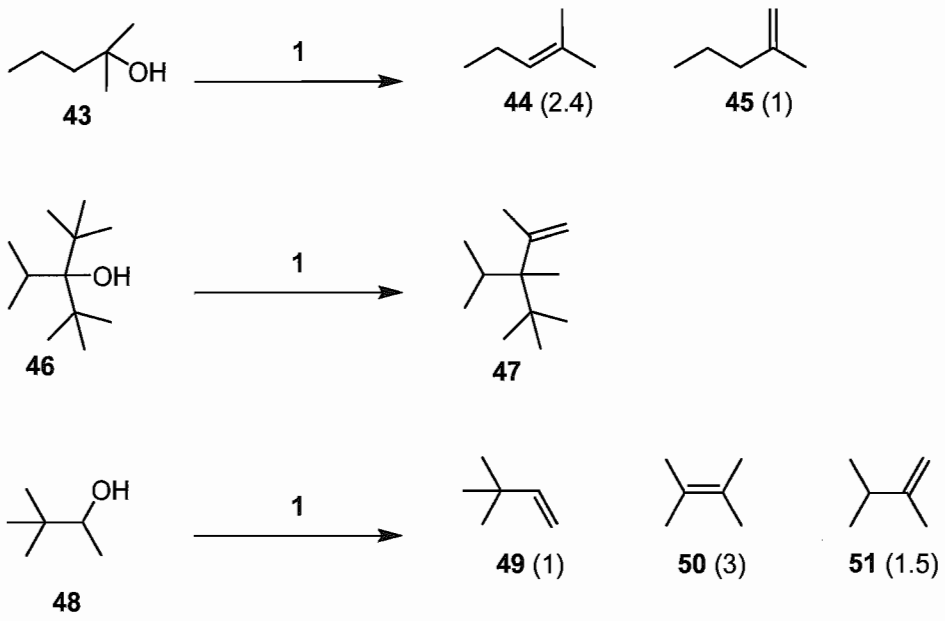



**Figure 10**-Dehydration of alcohols with stabilized carbocation intermediates (product ratio)

Following Burgess' work on dehydration reactions with **1**, several other reactions were reported. In 1988, Claremon and Phillips reported the dehydration of primary amides to nitriles with the Burgess reagent (Figure 11).[4]

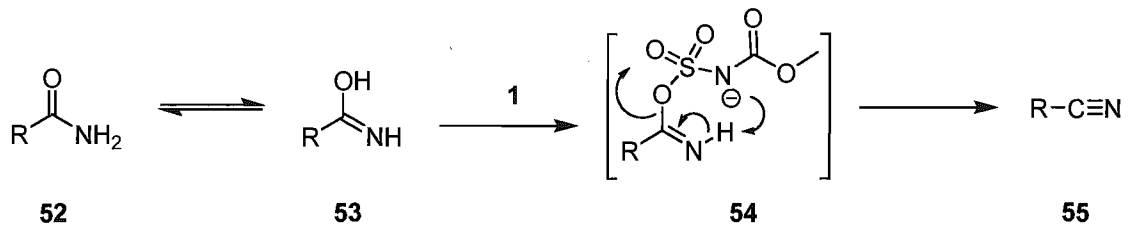



**Figure 11**-Dehydration of amides to nitriles with the Burgess reagent[4]

Prathapan and co-workers reported the synthesis of nitriles from *cis*-aldoximes with the Burgess reagent in 2000 (Figure 12).[5]

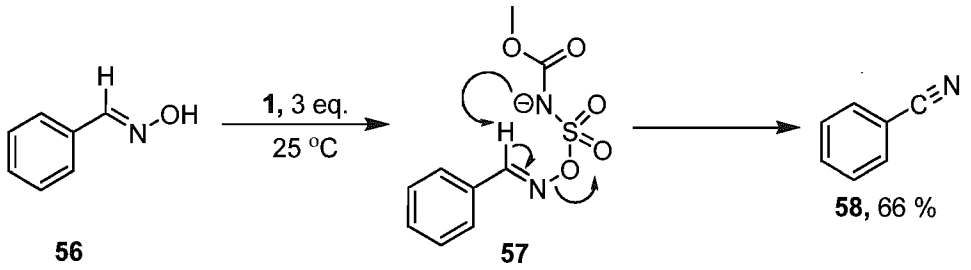



**Figure 12**-Conversion of *cis*-aldoximes to nitriles with the Burgess reagent[5]

McCarthy and co workers used the Burgess reagent to convert formamides to isocyanides (Figure 13).[6]

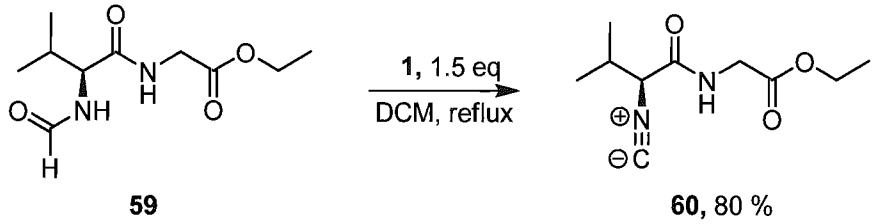
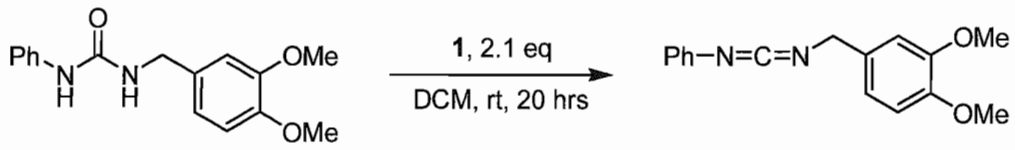



**Figure 13**-Synthesis of isocyanides from formamides[6]

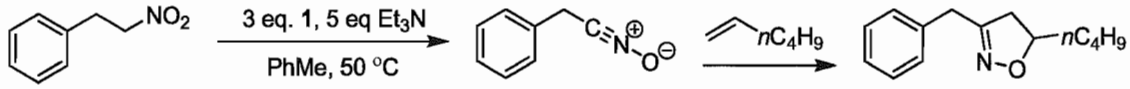
Building on the work of Claremon, Barvian and co-workers used the Burgess reagent to dehydrate ureas to carbodiimides in up to 91 % yield. These reactions were often clean enough not to require chromatography of the products (Figure 14).[7]




61 62, 91 %

**Figure 14**-Barvian's preparation of carbodiimides from ureas[7]

As part of a research project on milder conditions for the dehydration of primary nitroalkanes, Mioskowski and co-workers reported that the Burgess reagent worked under mild conditions (Figure 15).[8] However, they found diethylaminosulfur trifluoride (DAST) to be the best reagent for the dehydration of nitroalkanes.




63 64 65

**Figure 15**-Dehydration of nitroalkanes with Burgess reagent[8]

Burgess dehydrations are often milder than standard acid catalyzed dehydrations. Often, the Burgess reagent can effect a dehydration at temperatures lower than 70 °C.

### 2.1.2 Alternative reactions of the Burgess reagent

Since the 1990s reactions employing the Burgess reagent have been greatly expanded to include cyclodehydration reactions and non-dehydration reactions including the formation of heterocycles and various functional group interconversions.

Wipf and co-workers employed the Burgess reagent in a cyclodehydration reaction. β-Hydroxy-α-amino acids of type **66** were treated with Burgess reagent (**1**) to yield 4,5-dihydrooxazolines **68** (Figure 16).[9] When Mitsunobu conditions were used for this reaction, there were often side products, such as aziridines, formed.[10]

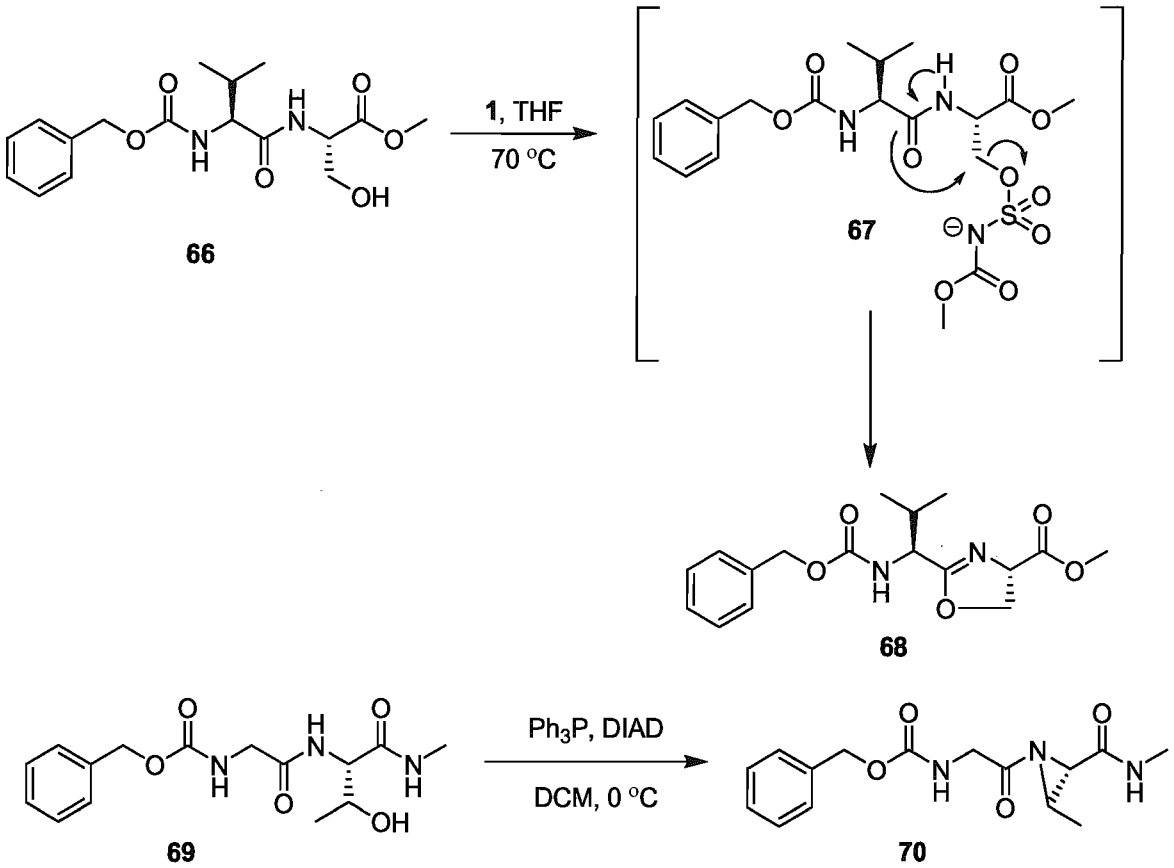
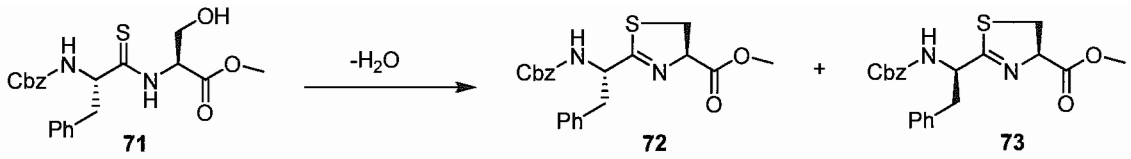



**Figure 16**-Cyclodehydration of β-hydroxy-α-amino acids with the Burgess reagent[9]

Wipf also applied this methodology to the formation of thiazoline peptide analogs (Figure 17).[11] The Burgess reagent gave the desired thiazolines in 96 % yield with 97:3 dr in about 10 minutes. The same reaction under other conditions, such as $TsCl/Et_3N$, $SOCl_2$/pyridine or Mitsunobu conditions, was lower yielding and led to extensive epimerization at the C-2 position.




| Conditions | Yield [%] | Ratio **72**:**73** |
|---|---|---|
| TsCl, $Et_3N$, DCM, 42 °C, 1 hr | 40 | 1:1 |
| 1. $SOCl_2$, 0 °C, 2 hr; 2. pyridine, THF, 0 °C, 15 min | 49 | 1:1 |
| $Ph_3P$, DIAD, DCM, -78 to 22 °C, 30 min | 80 | 78:22 |
| Burgess reagent (**1**), THF, 65 °C, 10 min | 96 | >97:3 |

**Figure 17**-Formation of thiazoline rings under various conditions[11]

Li employed the Burgess reagent as a cyclodehydration agent in the preparation of a series of *N*-bridged 5,6-bicylic pyridines.[12]

The Nicolaou group employed the Burgess reagent in the synthesis of several sulfone containing heterocycles.[13] In 2002, Nicolaou and co workers reported that the Burgess reagent could be used to synthesize sulfamidates from chiral 1,2 diols with excellent regio- and stereoselectivity.[14] The diols were prepared from styrene by the Sharpless asymmetric dihydroxylation and then treated with excess Burgess reagent yielding the cyclic sulfamidates. The sulfamidates were then hydrolyzed under acidic conditions to yield β-amino alcohols (Figure 18). The minor product was originally assumed to be regioisomer **76** but was later proven to be misassigned (See pages 15-16 for discussion of the structure correction).

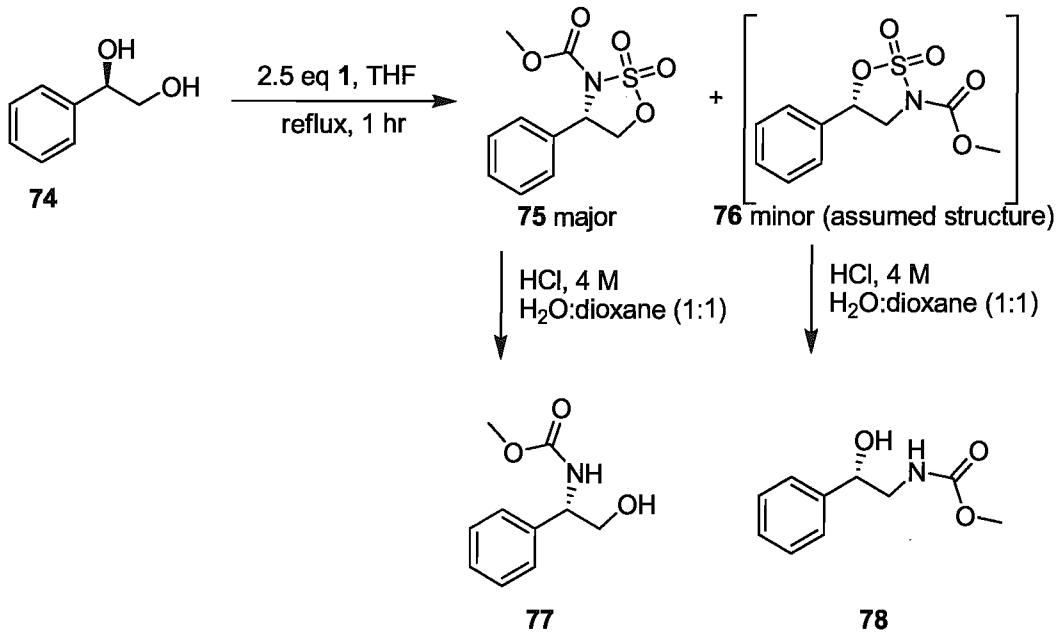



**Figure 18**-Formation of β-amino alcohols from styrene derived diols[14]

Nicolaou expanded on this methodology using the Burgess reagent to synthesize 5, 6, and 7-membered sulfamides from amino alcohols (Figure 19).[15]

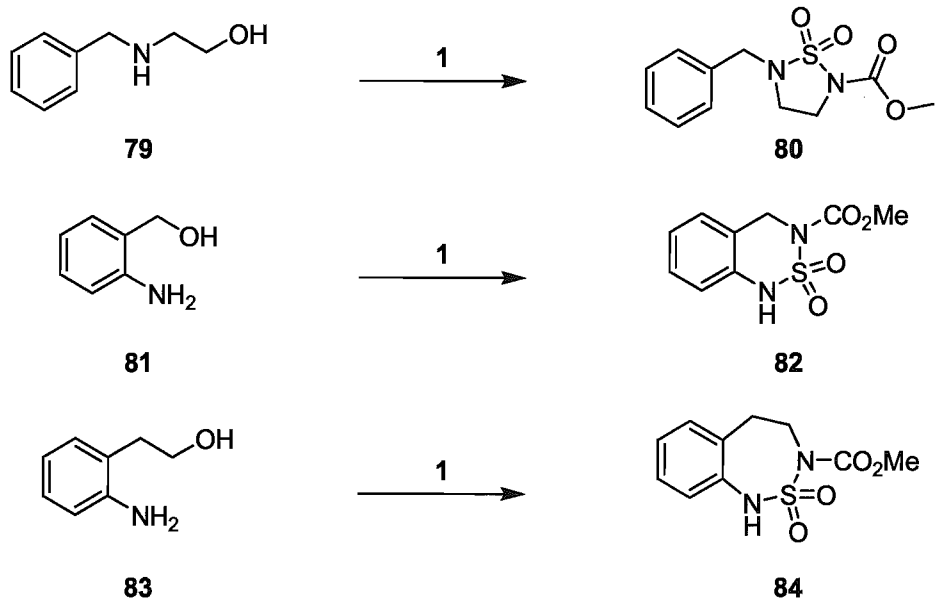



**Figure 19**-Synthesis of sulfamides from amino alcohols[15]

Nicolaou and co-workers applied their methodology to the synthesis of α- and β-glycosylamines (Figure 20).[16] The Burgess reagent was well suited to this chemistry because regio- and stereoselectivity are very predictable. For the preparation of α-glycosylamines **88**, 3,4,6-protected sugars **85** were treated with the Burgess reagent. The resulting sulfamidate **87** was then subjected to nucleophilic attack. β-Glycosylamines **92** were prepared from 2,3,4,6-protected sugars **89**. This reaction followed an $S_N2$ pathway similar to Burgess' early disclosures.

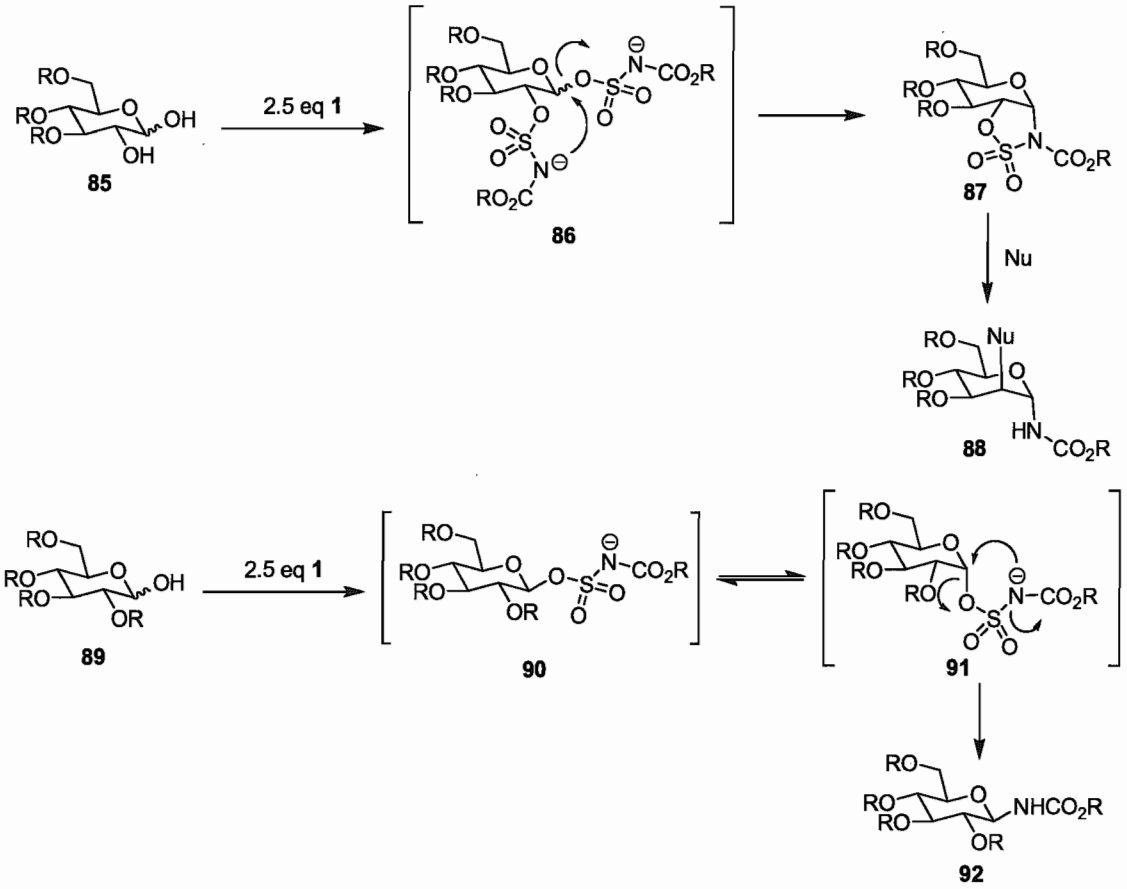



**Figure 20**-Nicolaou's synthesis of α- and β-glycosylamines[16]

While attempting the dehydration of the alcohol moiety in **93**, Raghavan and co-workers discovered that Burgess reagent reacts preferentially with sulfoxides to give sulfilimines **95** (Figure 21).[17] Initial reactions carried out at 60 °C in THF gave only

about 30 % yield. The reaction was optimized and was found to be high yielding when performed in benzene at room temperature. By varying the alkyl component of the Burgess reagent **98**, Raghavan was able to prepare several sulfilimines **97**.

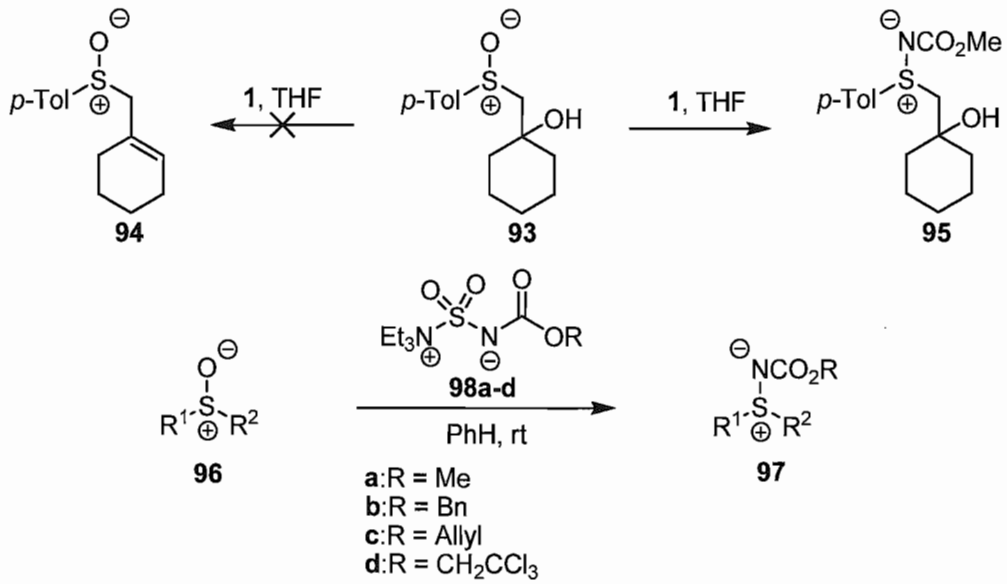



**Figure 21**-Formation of sulfilimines from sulfoxides[17]

Makara and co-workers treated a series of carboxylic acids with Burgess reagent to give mixed sulfcarboxyanhydrides of type **100** (Figure 22).[18] The mixed anhydrides could then be treated with amines to form amides **101** or acyl ureas **103**. Makara found that excess **1** was required with slow reactions due to decomposition of the Burgess reagent. The conversion of an acid to an amide or acyl urea could be completed in one pot as long as excess Burgess reagent was destroyed to prevent the formation of sulfamidates. This was accomplished by heating the reaction mixture to 80 °C for 15 minutes before the addition of the amine. The ratio of amide to acyl urea could be controlled by adjusting the temperature and employing microwaves as a heat source.

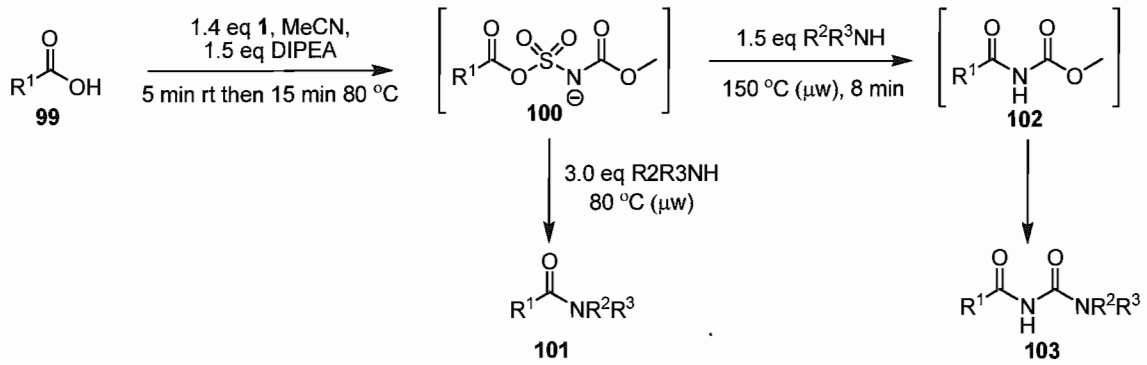



**Figure 22**-Preparation of acyl ureas and amides from carboxylic acids[18]

Until 2001, it was believed that the Burgess reagent was inert to epoxides. In his review in 2000 Lamberth stated, "The compatibility of the Burgess reagent with many functionalities, *e.g.* halogens, epoxides, alkenes, alkynes, aldehydes, ketones, acetals, esters, secondary amides, makes it an attractive technique for the introduction of C–C double bonds into highly functionalized molecules".[19] However, in 2003 Hudlicky and co-workers showed that the Burgess reagent reacted with epoxides to form cyclic sulfamidates. Lamberth cannot be blamed for the statement however, because several dehydration reactions had been performed on molecules containing epoxides with dehydration taking place preferentially to sulfamidate formation.[3,20]

In 2003, Hudlicky and co-workers showed that the Burgess reagent reacts with epoxides to form five or seven membered cyclic sulfamidates.[21] It was discovered that aliphatic epoxides formed only five membered sulfamidates while benzylic epoxides formed mostly seven membered sulfamidates with five membered sulfamidates being produced in about 2 % (Figure 23).

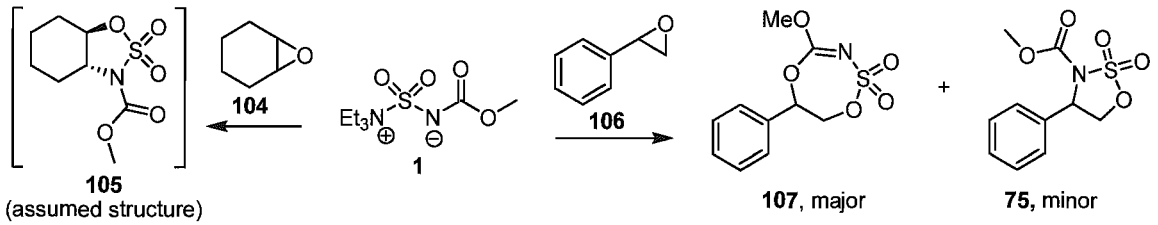



**Figure 23**-Formation of 5- and 7-membered sulfamidates from epoxides[21]

During subsequent work it was shown by Hudlicky that the five membered sulfamidate **105** which was initially thought to have a *trans*-stereochemistry was actually *cis* **109**.[22] A mechanism was proposed to account for the *cis* stereochemistry.[22] Hudlicky's proposed mechanism requires two equivalents of Burgess reagent and is similar to the mechanism Nicolaou proposed for the reaction of Burgess reagent with diols (Figure 24).[14]

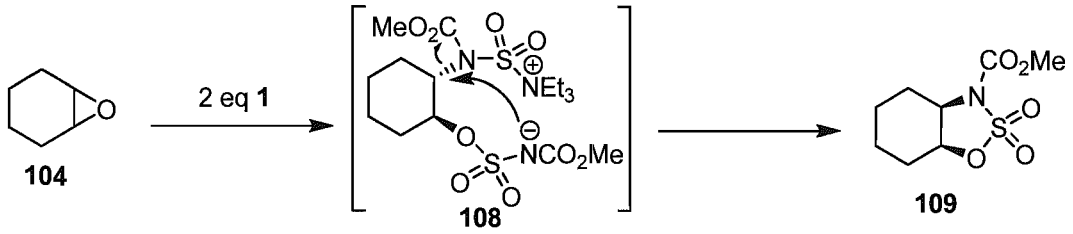
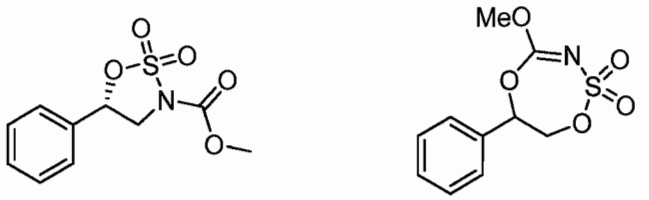



**Figure 24**-Hudlicky's proposed mechanism for the formation of *cis*-cyclic sulfamidates

Hudlicky also noted that the seven membered sulfamidate **107** formed from styrene oxide (**106**) was spectroscopically identical to Nicolaou's minor product (**76**, page 11, Figure 18) in the reaction of Burgess reagent with styrene diol **74**.[14] An X-ray crystal structure was acquired which proved that Nicolaou's minor product was indeed seven membered sulfamidate **107**.[21] A mechanism with degenerate pathways that accounts for the formation of both five and seven membered sulfamidates was proposed.



**76**, proposed structure **107**, actual structure

**Figure 25**-Correction of the structure of **76**

In another case of unexpected reactivity, Hudlicky and co-workers showed that when treated with Burgess reagent, thiols form disulfides (Figure 26).[23] Hudlicky had been attempting to expand the scope of Burgess dehydration and urethane formation to primary, secondary and tertiary thiols. However, when decane-1-thiol (**104**) was treated with Burgess reagent under standard conditions, disulfide **105** was isolated in nearly quantitative yield (Figure 26).

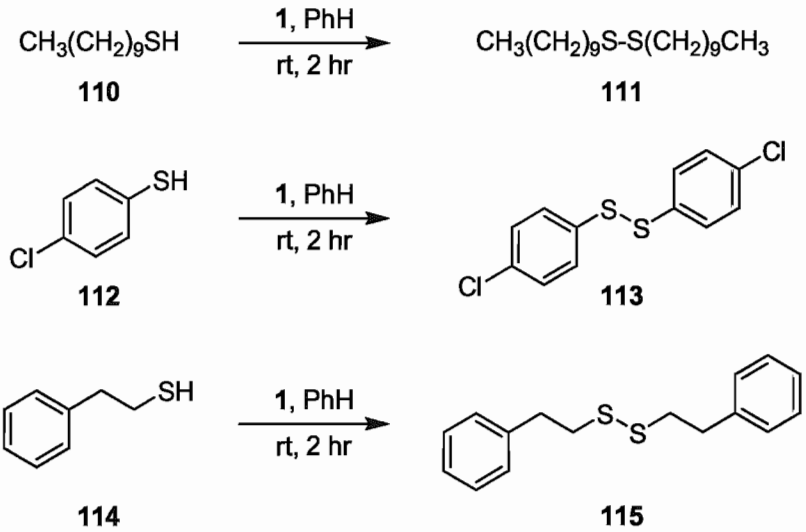
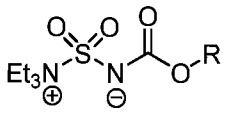


**Figure 26**-Formation of symmetrical disulfides from thiols[23]

### 2.1.3 Variants of the Burgess reagent

Several researchers have modified the alkyl or amine portions of the Burgess reagent for improved reaction characteristics or to incorporate different alkyl groups into their products. The Nicolaou group prepared variants of the Burgess reagent with

different alkoxy groups **98a-e** in their sulfamidate and sulfamide syntheses.[14-15] The methyl, benzyl, allyl, trichloroethyl, and *o*-nitro benzyl versions **98a-e** were employed in the synthesis of sulfamidates and the methyl, benzyl and allyl versions **98a-c** were used in sulfamide preparation. Raghavan employed Nicolaou's new Burgess reagents **98a-d** in his preparation of sulfilimines from sulfoxides.[17]

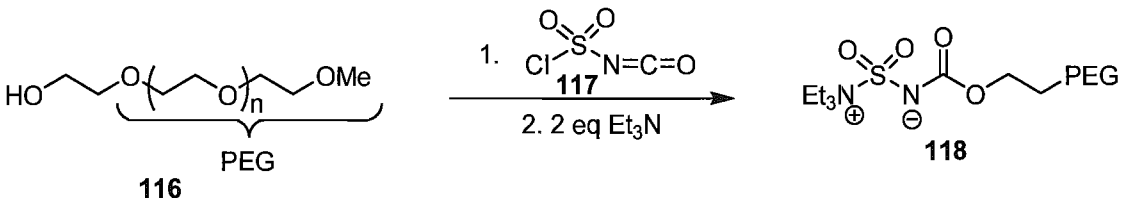


**98a-e**

**a**:R = Me
**b**:R = Bn
**c**:R = Allyl
**d**:R = $CH_2CCl_3$
**e**:R = *o*-$NO_2Bn$

**Figure 27**-Burgess reagents utilized by Nicolaou

Over the course of their studies of cyclodehydrations, the Wipf group noticed that the Burgess reagent decomposed upon exposure to moisture and oxidative conditions and that they obtained the best yields with freshly prepared Burgess reagent.[24] To improve the stability of the reagent, ease of handling and ease of purification of the products, Wipf developed a poly(ethylene glycol) (PEG) (**116**) linked version of the Burgess reagent **118** (Figure 28). They found that yields of oxazolines and thiazolines were 10-20 % higher when the PEG supported reagent was used in place of **1**. Upon completion of the reaction, filtration through a plug of silica often led to pure product as unreacted **118** and by-products remained absorbed in the PEG matrix or on silica gel.

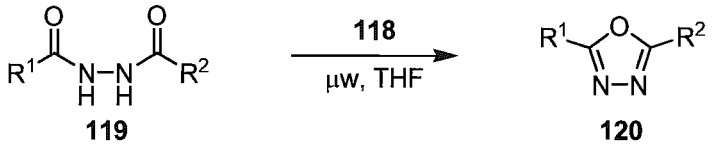


**116**

**Figure 28**-Wipf's preparation of PEG linked Burgess reagent **118**

Brain and co-workers employed Wipf's PEG supported Burgess reagent[24] in the synthesis of 1,3,4-oxadiazoles **120** from 1,2-diacylhydrazines **119** under microwave

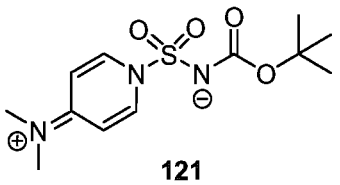
conditions (Figure 29).[25] Reaction times from two to four minutes under 100 W microwave conditions were noted. Building on Brain's work, Li and Dickson developed a one pot procedure for the synthesis of 1,3,4-oxadiazoles that proceeded in moderate to excellent yield at room temperature.[26]




119 120

**Figure 29**-Brain's synthesis of 1,3,4-oxadiazoles with PEG supported Burgess reagent[25]

While looking to develop a stable and efficient sulfamoylating reagent, Montero and co-workers developed reagent **121** (Figure 30).[27] Montero had been using chlorosulfonyl isocyanate (**117**) as a sulfamoylating reagent but found it was often too reactive. In order to reduce the reactivity, they treated it with *tert*-butanol and then DMAP. This led to Burgess type reagent **121**. Reagent **121** was shown to be an efficient sulfamoylating reagent giving products in moderate to high yields under mild conditions.



**121**

**Figure 30**-Montero's sulfamoylating reagent[27]

At the same time as Nicolaou was developing variants of the Burgess reagent for the formation of sulfamidates and sulfamides [14-15] the group of Wood independently developed the benzyl version of the Burgess reagent **98b** for a one step conversion of primary alcohols to Cbz protected amines.[28]

Masui and co-workers prepared a variant of the Burgess reagent by treating **117** with isopropanol and pyridine in a one pot procedure.[29] The reagent could then be treated

with dry or aqueous amines to form sulfamides (Figure 31). The advantage to Masui's methodology was that sulfamides could be produced from aqueous amines such as ammonia or methylamine at room temperature where traditional methods required anhydrous amines and low temperatures (either because of the low boiling point of the amine or exothermic reactions).

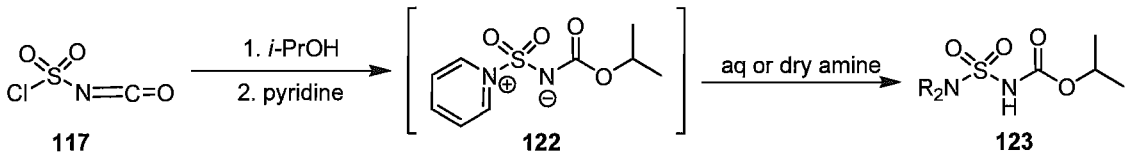



**Figure 31**-Masui's one pot preparation of sulfamides[29]

As part of their research in synthesizing sulfamidates from epoxides the Hudlicky group attempted to use C2 symmetric Lewis acid catalysts to form chiral sulfamidates of type **115** which could then be used to access chiral amino alcohols.[22] These attempts were unsuccessful and it was rationalized that the Lewis acid and the Burgess reagent could not coordinate simultaneously to an epoxides for steric reasons. Hudlicky then turned his attention toward creating a chiral auxiliary version of the Burgess reagent **124**. When cyclohexene oxide (**104**) was treated with **124** a 1:1 mixture of diastereomeric sulfamidates **125a-b** was produced (Figure 32). The mixture was separable by column chromatography and the diastereomeric sulfamidates could be treated to form *cis* or *trans*-amino alcohols in both enantiomeric series, the latter group of compounds produced by the reaction of *cis*-sulfamidates with ammonium benzoate.[30]

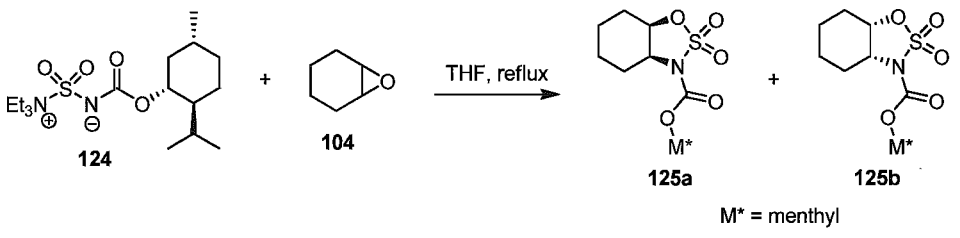
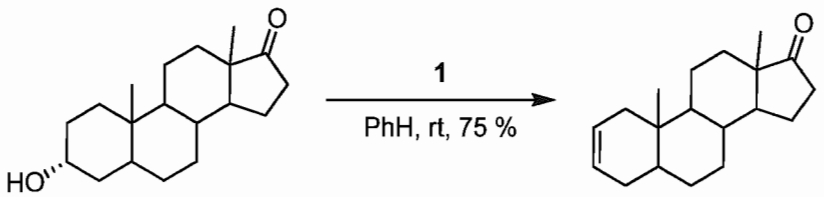



**Figure 32**-Reaction of Hudlicky's chiral auxiliary Burgess reagent with epoxides[22]

### 2.1.4 Applications of the Burgess reagent in total synthesis

The Burgess reagent has proven to be very useful in synthesis as a dehydrating agent due to its mild reaction conditions. The Burgess reagent is soluble in a wide variety of organic solvents and many reactions can be performed at room temperature at neutral pH. Its wide range of reactivity has led to its use in the syntheses of many complex natural products.

The first reported use of the Burgess reagent in synthesis was by Crabbe who reported the dehydration of several steroidal alcohols (Figure 33).[31] Caspi and co-workers also reported the dehydration of several steroidal alcohols to their corresponding olefins.[32]




**126** **127**

**Figure 33**-Dehydration of steroidal alcohols by Burgess reagent[31]

Stork employed the Burgess reagent in his general method for the synthesis of 11-oxygenated steroids (Figure 34).[33-35] The Burgess reagent was used to dehydrate **128** which then underwent an intramolecular Diels-Alder reaction. By this general method, Stork synthesized cortisone, adrenosterone, 11-ketoprogesterone, and 11-ketotestosterone. Dehydration of **128** with Burgess reagent led to the desired Diels-Alder precursor **129a** as well as the regio-isomer **129b**, which did not undergo cyclization and was therefore easily separated from the mixture. Further transformations of **130** led to **131**, which was identical to an authentic sample of silylated 11-ketotestosterone.

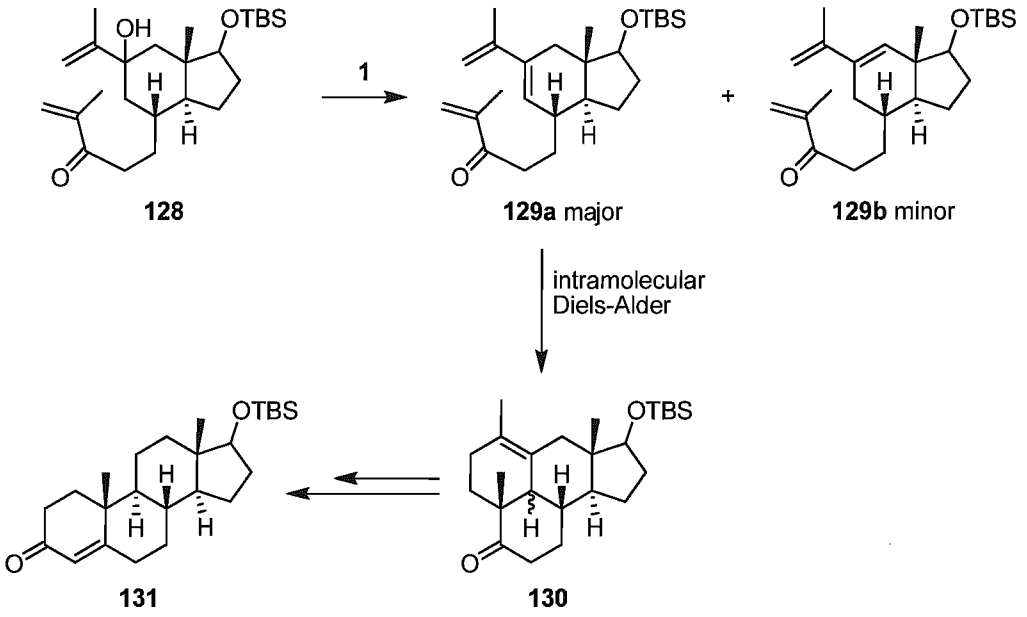



**Figure 34**-Application of Burgess reagent in Stork's ketosteroid synthesis

Rigby employed the Burgess reagent as a dehydrating agent in his syntheses of β-cedrene (**134**)[36] and (+)-narciclasine (**136**) (Figure 35).[37]

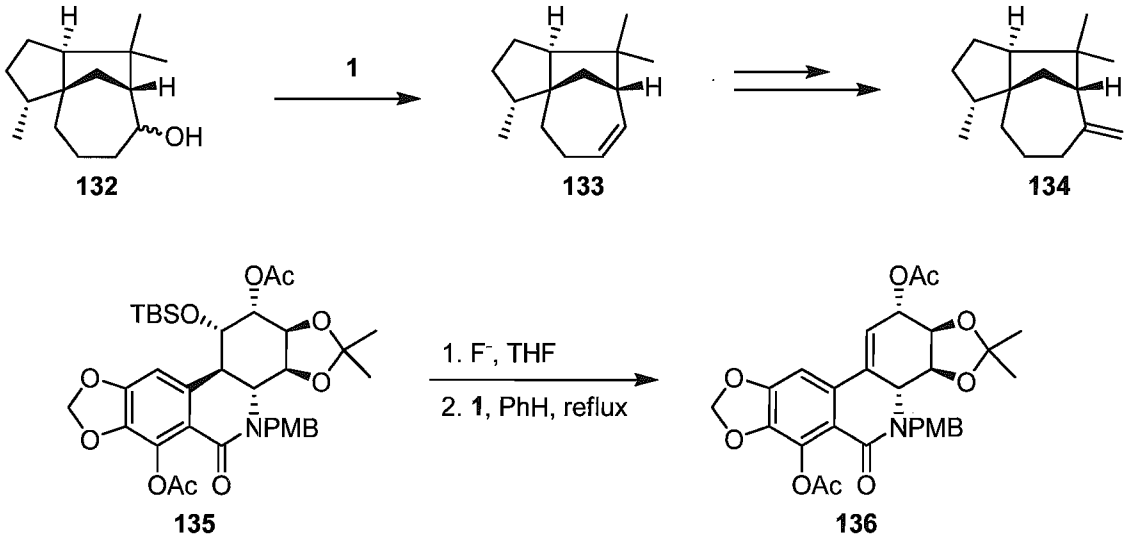



**Figure 35**-Rigby's use of the Burgess reagent in the syntheses of cedrene and narciclasine[36-37]

In the Kita group's synthesis of both enantiomers of the complex natural product fredericamycin A (**139**), a key step was the dehydration of alcohol **138** (Figure 36).[38] Kita first employed an *anti*-elimination under acidic conditions which was successful but only

in 51 % yield. They then attempted a Chugaev elimination which was unsuccessful. The Burgess reagent however, gave a clean elimination in quantitative yield.

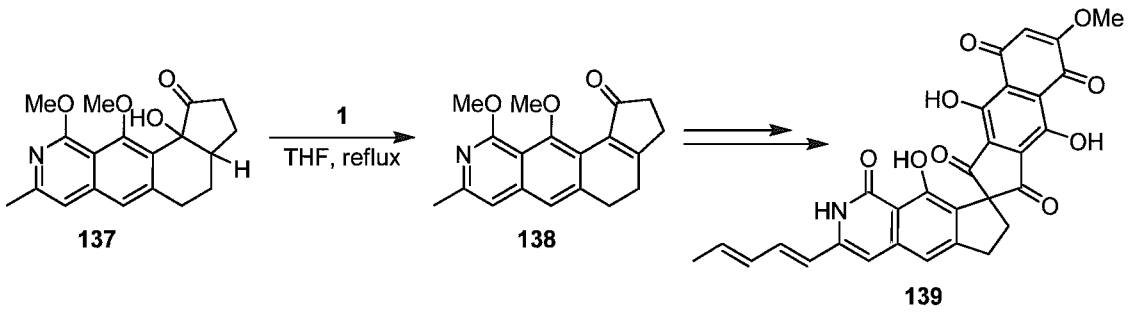



**Figure 36**-Use of the Burgess reagent in Kita's synthesis of fredericamycin A[38]

Recently, Ciufolini and co-workers have employed the Burgess reagent in their synthetic studies toward the terpenoid core of sordarin and analogs thereof.[39] Alcohol **140** was treated with Burgess reagent yielding Diels-Alder precursor **141** in 54 % (Figure 37). However, attempts at the Diels-Alder cyclization were unsuccessful and another route was followed.

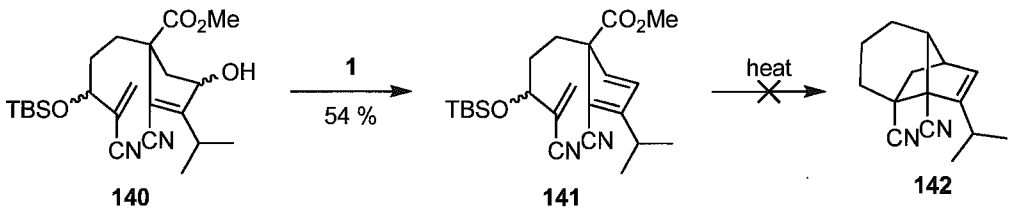



**Figure 37**-Use of the Burgess reagent in Ciufolini's studies toward the synthesis of sordarin[39]

Wipf's synthesis of (+)-curacin A (**146**) employed both the Burgess reagent (**1**) and PEG supported reagent **118**[24] in an elegant oxazoline-thiazoline conversion (Figure 38).[40-41] Deprotection of the silyl group of **143** proceeded in nearly quantitative yield. The resulting alcohol was subjected to cyclodehydration with Burgess reagent to give oxazoline **144**. Thiolysis followed by cyclodehydration with Burgess reagent (**1**) gave the natural product **146**. When PEG supported Burgess reagent **118** was employed in thiazoline formation, a modest increase in yield was observed.

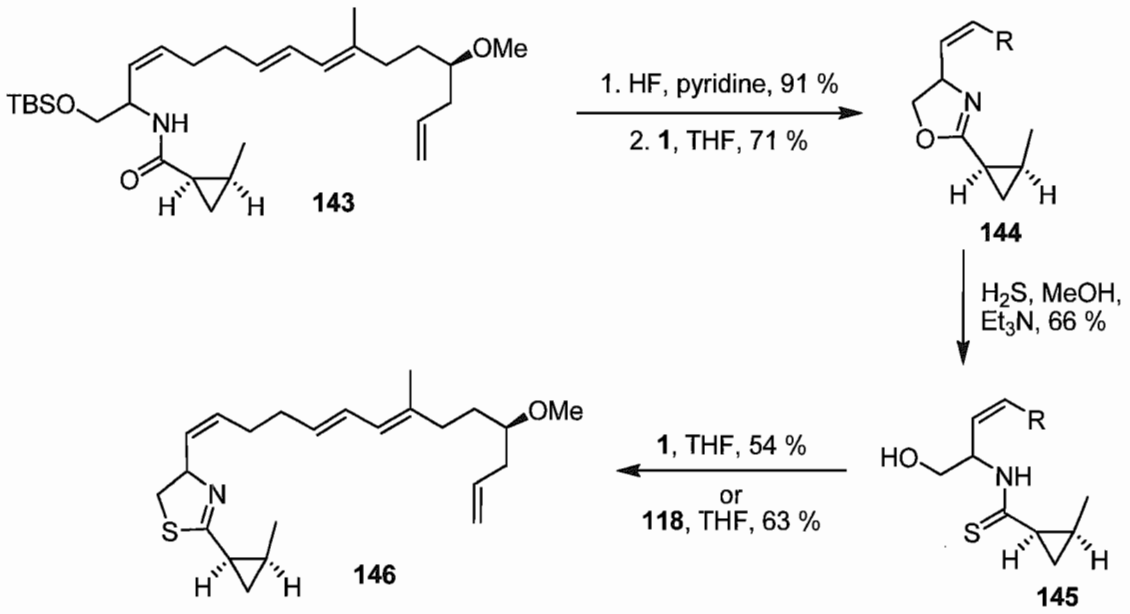



**Figure 38**-Application of Burgess cyclodehydration in the synthesis of (+)-curacin A[41]

Wipf also employed Burgess cyclodehydrations and oxazoline-thiazoline conversions in the first total synthesis of (-)-thiangazole[42] and the complex marine natural product lissoclinamide 7.[43] Wipf's Burgess cyclodehydration methodology was also employed in Ino's synthesis of yersiniabactin [44], Wipf's syntheses of westiellamide [45] and hennoxazole A [46], and Miller's synthesis of the peptide fragment of pseudobactin.[47]

Raghavan and co-workers demonstrated the synthetic utility of their sulfilimine formation methodology with benzyl Burgess reagent **98b** by applying it to the total syntheses of (-)-deoxocassine (**150**) and (+)-desoxoprosophylline (**151**).[48-49] Sulfoxide **147** was treated with the benzyl Burgess reagent **98b** to yield sulfilimine **148**. The sulfilimine was then used as an internal nucleophile to give common intermediate **149** which was transformed to natural products **150** and **151** (Figure 39).

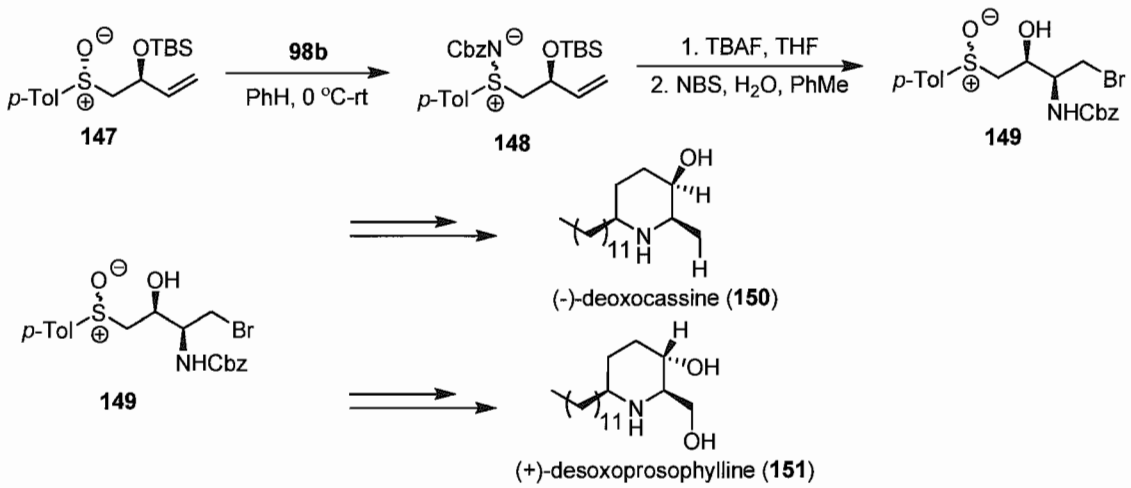



**Figure 39**-Raghavan's syntheses of (-)-deoxocassine and (+)-desoxoprosophylline[48-49]

Hudlicky and co-workers employed their chiral auxiliary Burgess reagent **124**[22] in an enantiodivergent formal synthesis of the fungal metabolite (+)- and (-)-balanol (**155**).[30,50] The key step was a regioselective opening of epoxide **152** (Figure 40).[22] The resulting diastereomeric sulfamidates **153a** and **153b** were separated by column chromatography and opened with benzoate to give the *trans*-amino alcohol moiety. These were then further elaborated to formal intermediates of (-)- and (+)-balanol, **154a** and **154b** respectively.

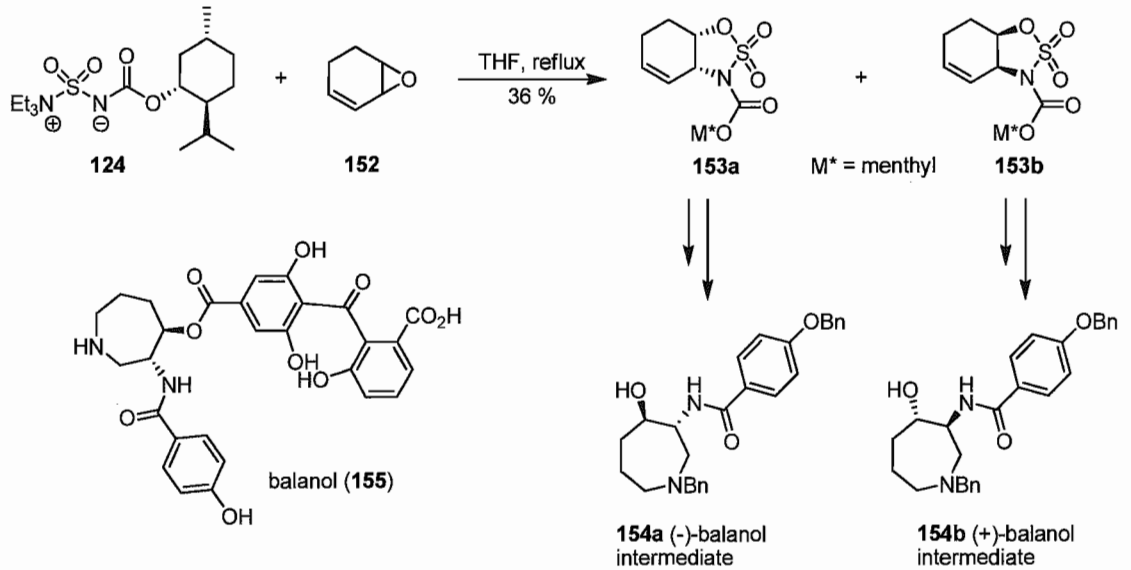



**Figure 40**-Hudlicky's enantiodivergent formal synthesis of balanol[30]

Since its discovery the Burgess reagent (**1**) has been widely used for dehydration reactions in the synthesis of complex natural products. Burgess dehydrations are usually high yielding and side reactions are rare. Renewed interest in the Burgess reagent over the last twenty years has led to the development of new reactions as well as new versions of the reagent further expanding the versatility of this already useful reagent.

## 2.2 Morphine

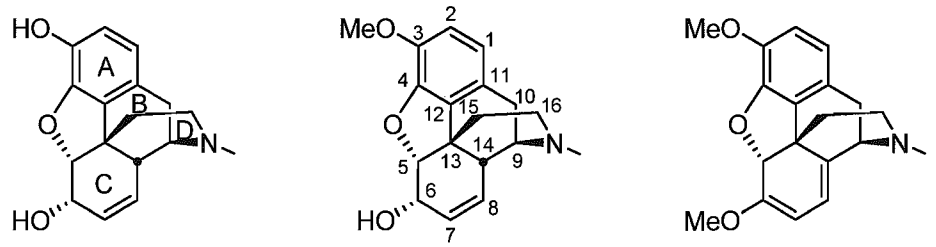
### 2.2.1 Historical uses, isolation, and biosynthesis

Morphine (**3**) has been used by humans as an analgesic, antitussant and recreational drug for thousands of years. The first recorded use of opium was by the Sumerians in about 3400 BC.[51-52] Opium poppies (*Papaver somniferum*) appeared in Egyptian artwork and the Greek and Roman gods of sleep were often depicted with poppies. The Swiss physician Paracelsus developed a preparation of opium and other ingredients in wine and sold it as a remedy and sleep aid. In Great Britain, several tinctures of opium in alcohol were marketed as cough suppressants and sleep aids which were frequently administered to children to quiet them. These remedies were sold under names such as Street's Infants' Quietness, Atkinson's Infants' Preservative, and Mrs. Winslow's Soothing Syrup.

The British East India company was brought back from the verge of bankruptcy by sales of Indian opium to China. The Chinese attempted to prohibit the sales and use of Opium in 1839. However, smugglers and American ships still supplied Indian opium to China. In 1839, Chinese officials took several British ships hostage and confiscated over 20,000 chests (1,600 tons). This led British foreign secretary Lord Palmerston to initiate war. The goals of the British Crown were to obtain reparations for the insults suffered by captured British sailors and officials, to recover the lost revenue from the opium seized by the Chinese and assure the security of British merchants in China. The British easily defeated the Chinese and the treaty ending the war opened up four ports to British merchants and ceded Hong Kong to Queen Victoria. The first Opium War, however, did not fully resolve the dispute over opium trade. Throughout the 1840's and early 1850's

the British sought to legalize the opium trade under the pretense that the Chinese could not regulate the illicit opium trade as effectively as the British. The second Opium war, also known as the Arrow war, began when Chinese officials boarded the British registered ship Arrow whose crew was accused of smuggling and piracy in 1856. The war ended with a treaty legalizing the import of Indian opium in 1858. At the time of the Arrow war, a strong anti-opium trade movement was growing in England. In the late nineteenth and early twentieth century, British India became less dependent on opium revenue and an anti-opium movement began to take hold in China. This led to a series of reductions in opium shipment to China and in 1913, the Indian government stopped all opium shipments to China.[52-53] While use of raw opium continues today, most illicit opium is converted to heroin which is less bulky, thus facilitating transport.[54]

In 1805, the German pharmacist Serturner isolated morphine from raw opium.[55-56] The name morphine comes from Morpheus, the Greek god of dreams. The structure of morphine eluded scientists for over one hundred years and its elucidation was reviewed by Butora and Hudlicky.[57] The correct structure of morphine (Figure 41) was reported in 1925 by Robinson and Gulland[58] and was confirmed by Gates when he published the first total synthesis of morphine in 1952.[59]




morphine (**3**) codeine (**156**) thebaine (**157**)

**Figure 41**-Structure of morphine and related alkaloids

Opium is isolated from poppies by scoring the unripe seed pods of *P. somniferum* approximately 98 days after germination. The latex oozes out and is collected. A single seed pod can be harvested several days in a row.[52] The timing of the opium harvest is important because morphine alkaloids are produced for only a short time. As the seed pod ripens, alkaloid production stops and the alkaloids are broken down.[52] While this method is still used in places with more primitive farming techniques, most modern commercial poppy farms simply harvest the entire plant which is then sold to manufacturers as opium straw from which the alkaloids are extracted on a large scale.[52] The highest concentration of alkaloids is found in the seed pods but thebaine can be found in significant quantities in the roots of the opium poppy.[52,60]

The biosynthesis of morphine and related alkaloids has been elucidated (Figure 42). All carbon atoms present come from two molecules of the naturally occurring amino acid tyrosine (**158**). Nature provides an elegant solution to the synthesis of these complex molecules that is unrivalled by even the most efficient laboratory synthesis.

In the first stage of biosynthesis, one molecule of tyrosine is converted to dopamine (**159**) by the action of tyrosine decarboxylase and phenol oxidase. A second molecule of (**158**) is converted to 4-hydroxyphenylacetaldehyde (**160**). Dopamine (**159**) and 4-hydroxyphenylacetaldehyde (**160**) are then condensed to form (*S*)-norcoclaurine (**161**) by the action of norcoclaurine synthase. Subsequent methylation and oxidation give (*S*)-reticuline (**162a**) which is then epimerized to (*R*)-reticuline (**162b**) via the 1,2-dehydroreticulinium ion (**163**). A microsome bound cytochrome P450 containing enzyme then couples carbon atoms 12 and 13 forming salutaridinol (**164**).[61] The ketone at the C-7 position of salutaridinol is then reduced and acetylated. The free hydroxy group on C-4

then attacks, displacing the acetate in a $S_N2'$ reaction to give thebaine (**157**). Thebaine is then demethylated by thebaine 6-*O*-demethylase to neopinone (**165**)[62] which exists in an equilibrium with codeinone (**166**). Reduction of the C-6 ketone by codeine reductase[63-64] yields codeine (**156**) which is then demethylated by codeine-*O*-demethylase to morphine (**3**).[62]

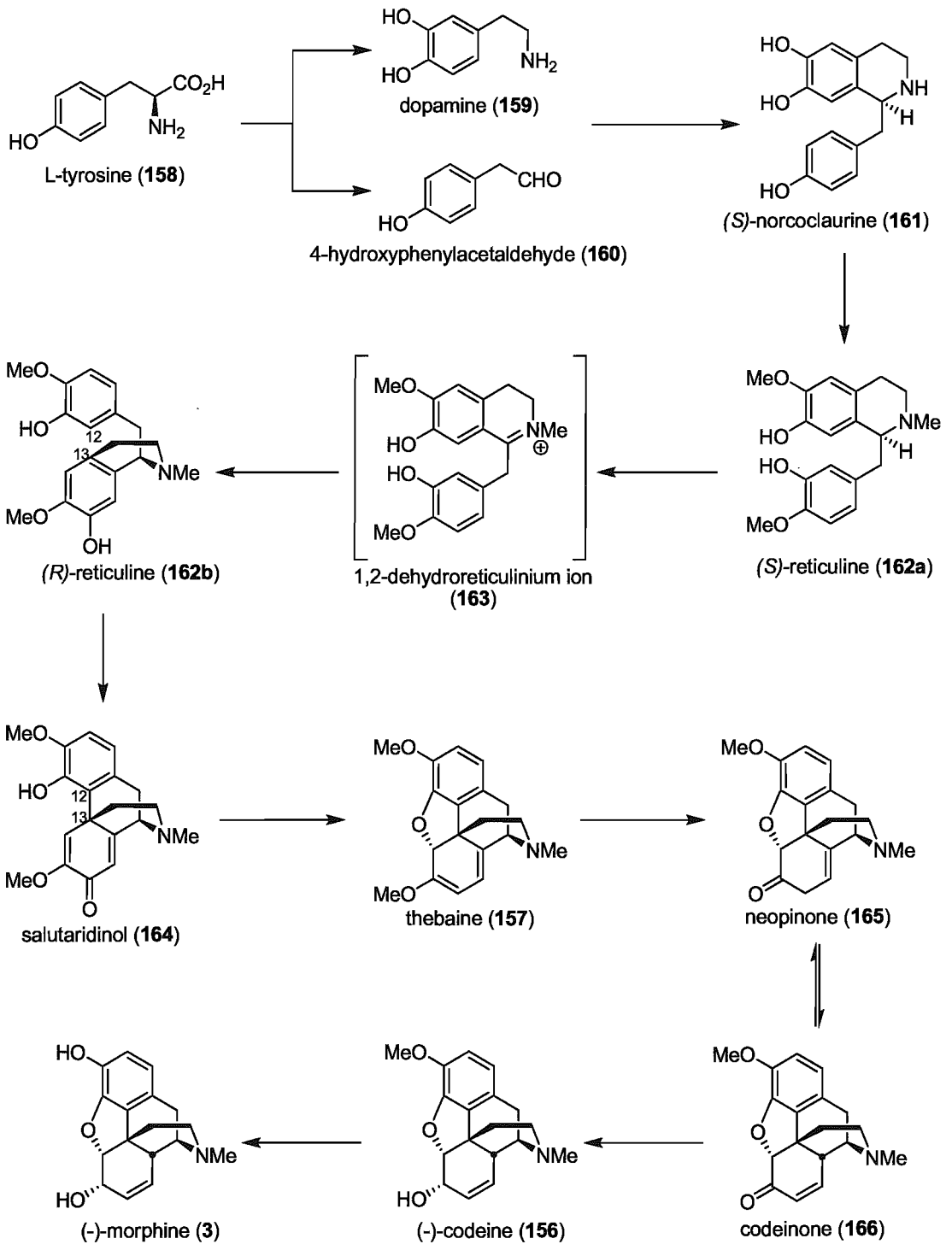



**Figure 42**-Biosynthesis of morphine

Thebaine (**157**) can also be converted to morphine (**3**) by an alternate pathway that accounts for the formation of trace amounts of oripavine (**167**) found in opium

(Figure 43).[62] In this alternate pathway, thebaine is converted to oripavine by the action of codeine-*O*-demethylase. Thebaine 6-*O*-demethylase then converts oripavine to morphinone (**168**) which is in turn converted to morphine by codeine reductase.

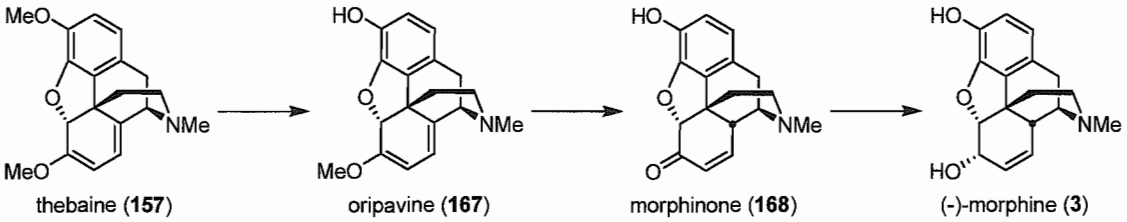



**Figure 43**-Alternate pathway for the conversion of thebaine to morphine[62]

### 2.2.2 Notable syntheses of morphine

#### Gates (1952)[59]

Gates published the first total synthesis of morphine (**3**) in 1952 thus confirming the structure proposed by Robinson and Gulland twenty seven years earlier.[58] Gates prepared both enantiomers of morphine via a resolution of intermediate **176**. Gates' synthesis was achieved in twenty four steps from 2,6-dihydroxynapthalene (**169**) with an overall yield of 0.01 %. As shown in Figure 44, an iterative nitrosation / reduction / oxidation procedure was used to transform 2,6-dihydroxynapthalene (**169**) into intermediate **172**. The nitrogen atom was installed by a Michael type addition of ethyl cyanoacetate to **172**. This was followed by base hydrolysis and decarboxylation to give **173**. The C-ring of the morphine skeleton was installed by a Diels-Alder reaction between **173** and butadiene. The D-ring was completed by a reductive cyclization yielding keto-lactam **175**. Reduction of **175** followed by methylation of the nitrogen atom gave **176** which contains all of the carbon atoms in morphine. At this stage a resolution was performed by crystallization of the tartrate salts of **176**. The C-6 position was hydroxylated in dilute sulfuric acid. Treatment with potassium hydroxide led to the

demethylation of the ether at C-4. The C-6 hydroxyl group was then oxidized to ketone **177**.

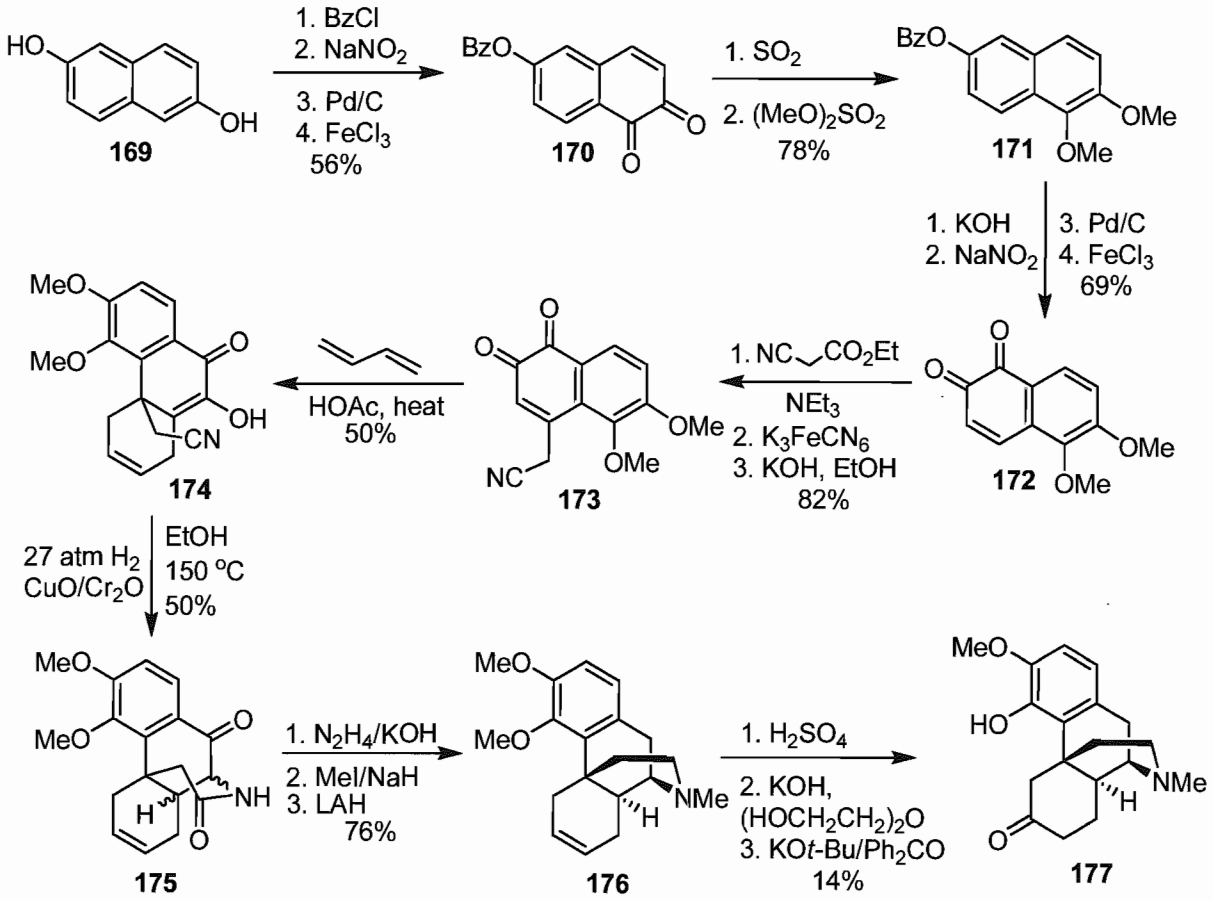



**Figure 44**-Gates' synthesis of intermediate **177**[59]

After the tartrate resolution of **176**, the stereochemistry was correct at positions C-9 and C-13 but epimeric at C-14. Compound **177** was treated with bromine in acetic acid. Elimination of HBr gave an α,β-unsaturated ketone which was converted to its hydrazone **179a**. Hydrazone **179a** then equilibrated to the more stable cis fused ring system **179b** (Figure 45).

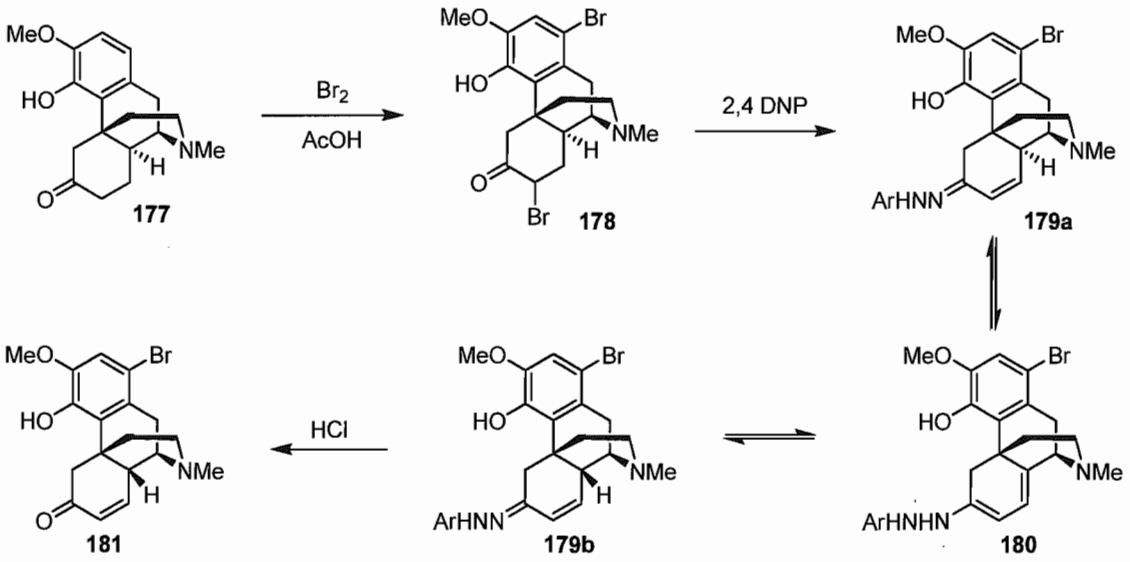



**Figure 45**-C-14 epimerization[59]

After the epimerization at C-14 was complete, hydrogenation of α,β-unsaturated ketone **181** gave the precursor for the closure of the C-4,C-5 dihydrobenzofuran ring **182.** Repetition of the conditions for the epimerization of C-14 allowed for the closure of the furan ring and installed the C-7, C-8 unsaturation. Acid hydrolysis of phenylhydrazone **183** followed by reduction with lithium aluminum hydride gave codeine (**156**) in 27 % over two steps. Demethylation using Rappoport's conditions[65] gave morphine (**3**) in 35 % yield (Figure 46).

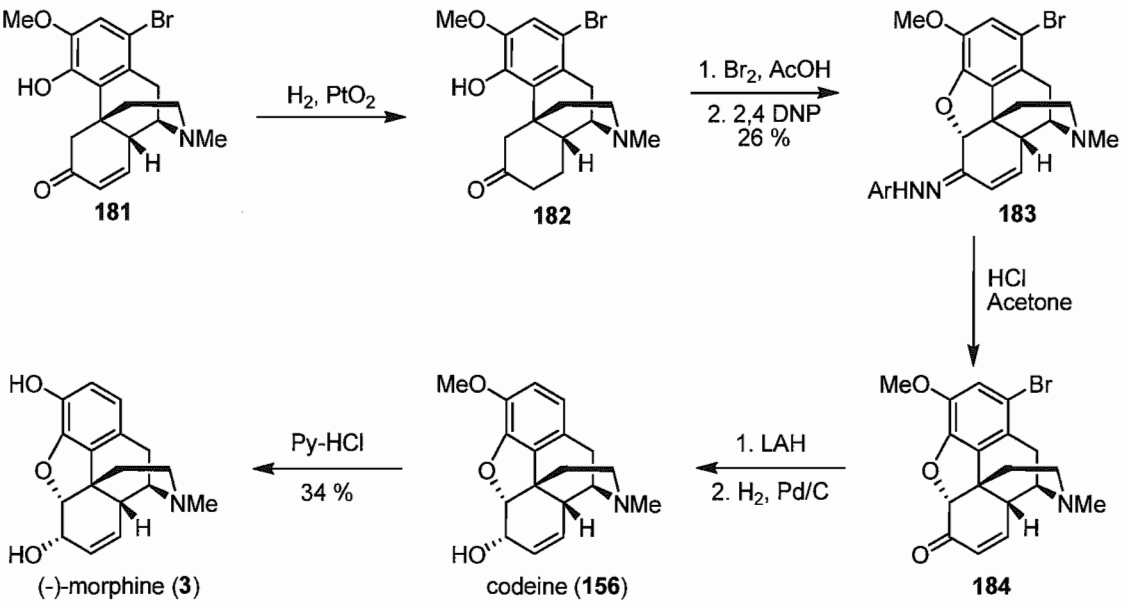



**Figure 46**-Final transformations in Gates' synthesis of morphine[59]

## Rice 1980[66]

Rice's formal synthesis of morphine (**3**) in 1980 is noteworthy as it is the shortest and the highest yielding synthesis to date. Rice's synthesis allows for the synthesis of both the natural and unnatural enantiomers of hydrocodone. The route is biomimetic and involves the isolation of only six intermediates, requires no chromatography and the final yield of formal intermediate hydrocodone (**185**) is an amazing 29 %.

The synthesis begins with the condensation of amine **186** and acid **187** followed by a Bischler-Napieralski reaction to give **188**. Intermediate **188** was then resolved with (*S*)-(-)-α-methylbezyl isocyanate. Birch reduction of the more electron deficient aromatic ring followed by formylation, protection and bromination gave cyclization precursor **190**.

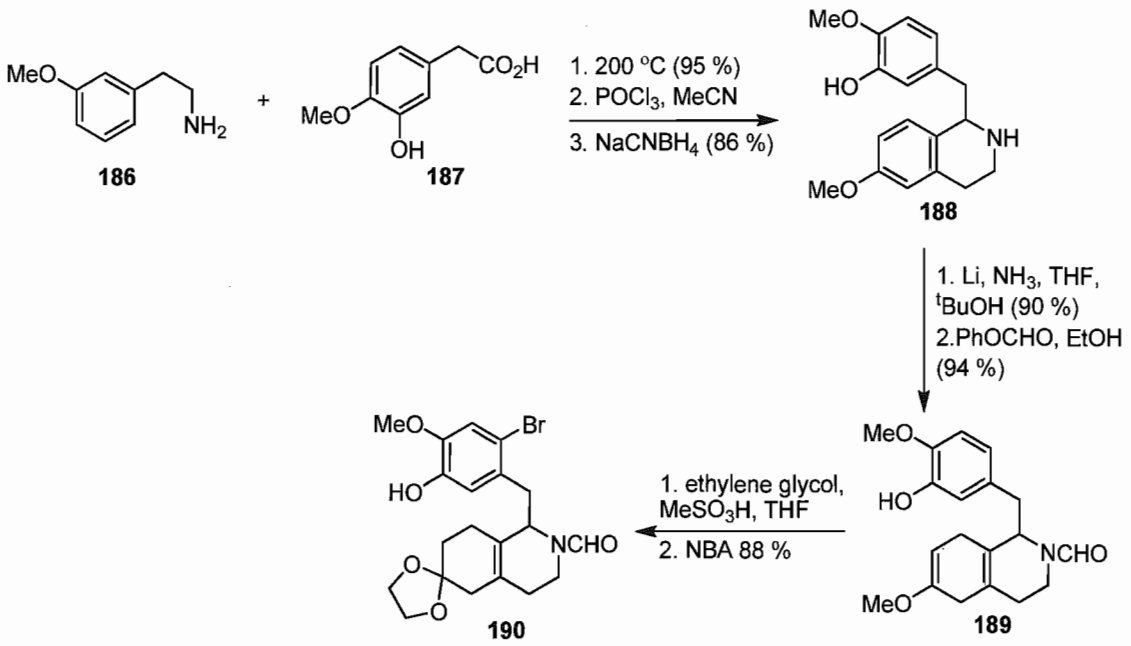



**Figure 47**-Rice's synthesis of cyclization precursor **190**

Hydrolysis of **190** with formic acid followed by a hydrogen fluoride mediated Grewe-type cyclization gave the skeleton of morphine in 60 % yield. Acid hydrolysis of formamide **191** gave 1-bromo-nordihydro-thebainone (**192**). 1-Bromo-nordihydro-thebainone (**192**) was then converted to hydrocodone (**185**) by a four step sequence that proceeded in 79 % yield. The bromine at C-1 was removed by hydrogenation, the dihydrobenzofuran ring was closed by alpha bromination of the ketone and base induced ring closure. Removal of the aryl bromide and methylation of the nitrogen atom were achieved by hydrogenation over palladium on carbon in the presence of acetic acid and formaldehyde. When **192** was subjected to hydrogenation without the addition of formaldehyde, norhydrocodone (**193**) was isolated.

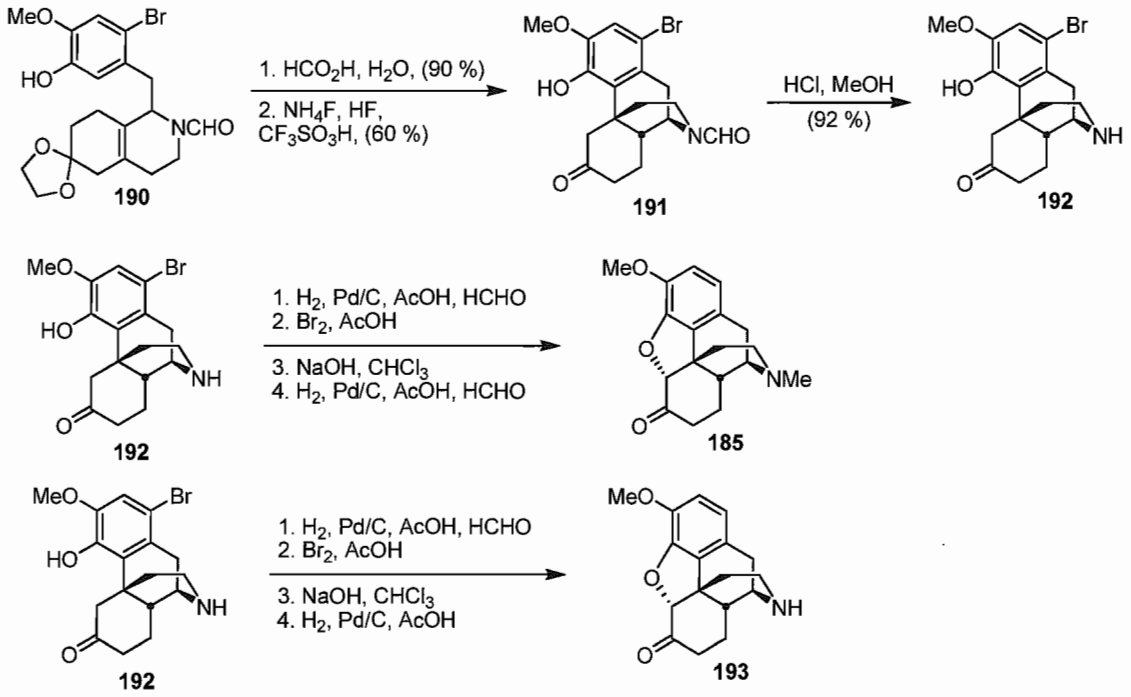



**Figure 48**-Final transformations in Rice's formal synthesis of morphine

## Hudlicky 2009[67]

Hudlicky's 2009 enantiodivergent synthesis of codeine (**156**) is based in part on Parker's strategy used in the synthesis of morphine[68-69] and employs a Heck coupling similar to Trost's synthesis.[70-71] Hudlicky's synthesis (Figure 49) begins with the enzymatic dihydroxylation of β–bromoethyl benzene (**194**) to diol **195**. Diol **195** was subjected to diimide reduction and the hydroxyl groups were acetate protected. Protected diol **196** was treated with methylamine and potassium carbonate to give a secondary amine which was protected as a Boc carbamate **197** without purification. The distal hydroxyl group was protected as a silyl ether. A Mitsunobu reaction between alcohol **198** and bromoisovanillin (**199**) gave intermediate **200** which was the substrate for the first Heck reaction.

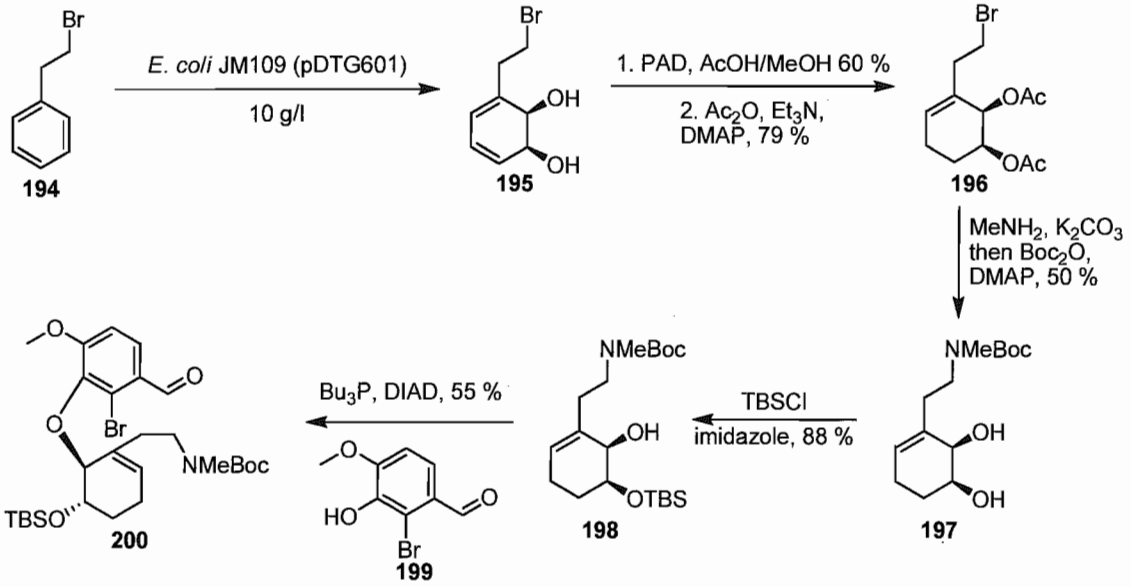



**Figure 49**-Hudlicky's synthesis of intermediate **200**[67]

The intramolecular Heck reaction gave cyclized product **201** in 82 % yield. A Wittig reaction was used to convert the aldehyde to a vinyl bromide. Bromide **202** was subjected to a second intramolecular Heck reaction to complete the phenanthrene core of codeine. The C-6 stereochemistry was inverted by a desilylation followed by an oxidation/reduction procedure. Deprotection of the Boc carbamate gave **204**, the enantiomer of Trost's intermediate.[70] Hudlicky attempted to repeat Trost's hydroamination procedure but was unsuccessful. To convert Trost's intermediate to codeine, Hudlicky used an oxymercuration procedure which gave *ent*-**156** in 18 % yield (Figure 50).

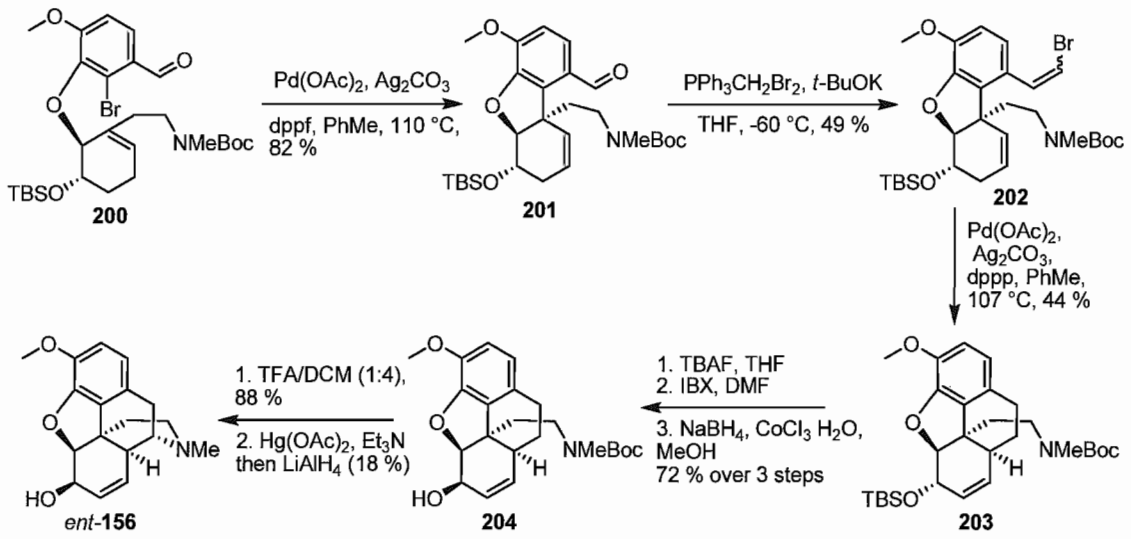



**Figure 50**-Hudlicky's transformation of **200** to *ent*-codeine[67]

Originally, Hudlicky's strategy for the synthesis of the natural isomer of codeine was to perform two sequential Mitsunobu reactions despite low yields in a similar sequence.[72] The first Mitsunobu reaction would invert the C-5 stereochemistry and the second reaction would invert again and couple the A-ring fragment (**199**). This strategy was found to be very low yielding so an alternate path was taken. Hudlicky performed a Mitsunobu reaction on **197** using Banwell's procedure.[73] The distal hydroxyl group was then converted to tosylate **206**. Hydrolysis of the ester, followed by displacement of the tosylate, gave epoxide **207**. The epoxide was then opened with the potassium salt of bromoisovanillin (**208**). The hydroxyl group was protected as a silyl ether to give the enantiomer of **200**. The procedure shown in Figure 50 was then followed to convert *ent*-**200** to the natural isomer of codeine (**156**) (Figure 51). Hudlicky's 2009 synthesis is noteworthy in that it can be used to synthesize both the natural and unnatural isomers from a single starting material without a resolution. This overcomes one of the criticisms of the use of enzymatic reactions to produce synthons in that only one enantiomer is

produced thus limiting chemists to the synthesis of only one enantiomer of a natural product.

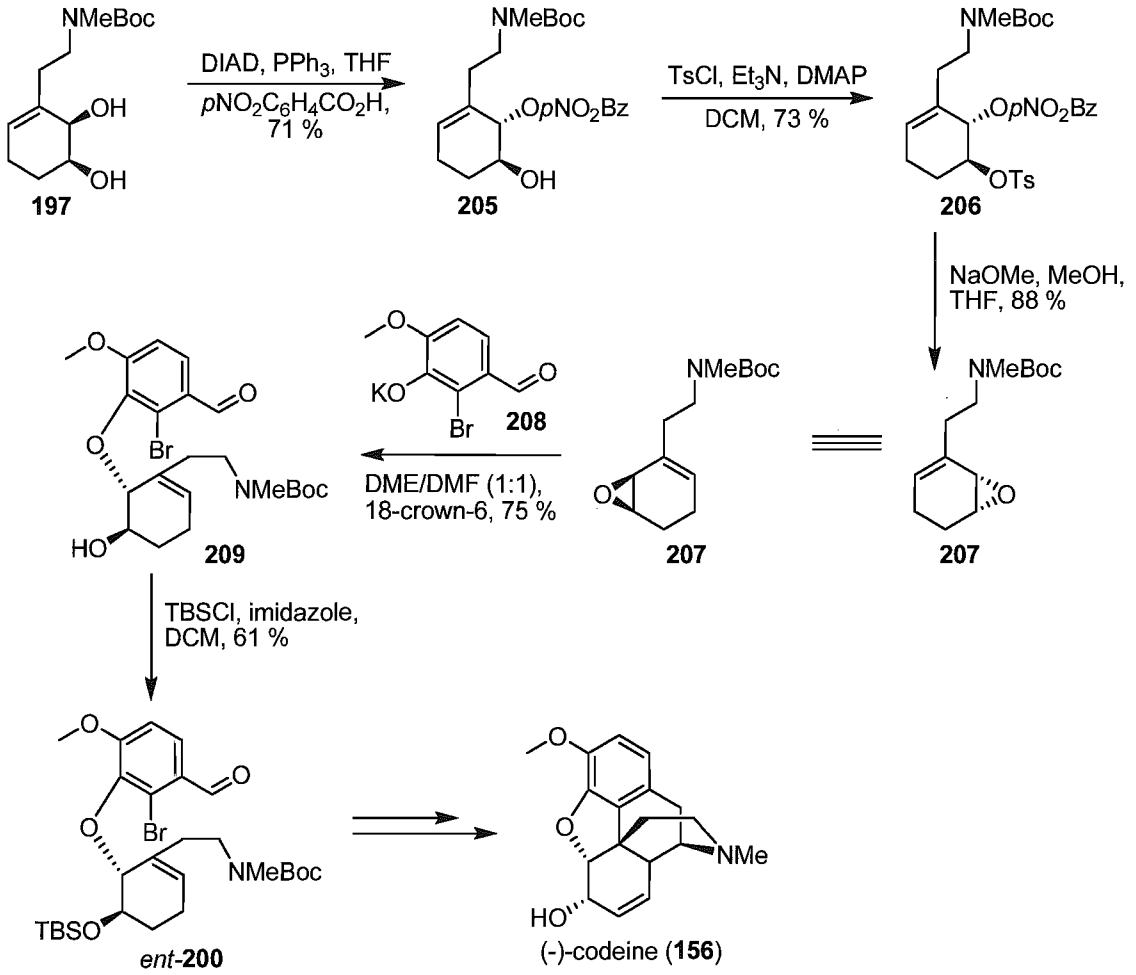



**Figure 51**-Hudlicky's synthesis of the natural enantiomer of codeine[67]

## Chida 2008[74]

Chida's formal synthesis of morphine employed a cascade Johnson-Claisen rearrangement to set the C-13 quaternary center. The Claisen rearrangement was catalyzed by 2-nitrophenol and is similar to a rearrangement he employed in his synthesis of the *Amaryllidaceae* alkaloid galanthamine.[75]

Chida's synthesis begins with tri-*O*-acetyl-D-glucal (**210**) which is deacetylated and reprotected in a sequence with a yield of 45 % over three steps. Cleavage of the

*p*-anisaldehyde acetal and replacement of the alcohol gave iodide **212**. Elimination of the iodide to an olefin gave the substrate for a Ferrier's carbocyclization, **213**. The cyclization was followed by β-elimination to give cyclohexenone **214** and proceeded in 91 %. L-Selectride® was employed for a 1,4 reduction and the resulting enolate was trapped as a vinyl triflate **215**. Suzuki coupling to A-ring fragment **8** and subsequent deprotection gave Claisen rearrangement substrate **218**.

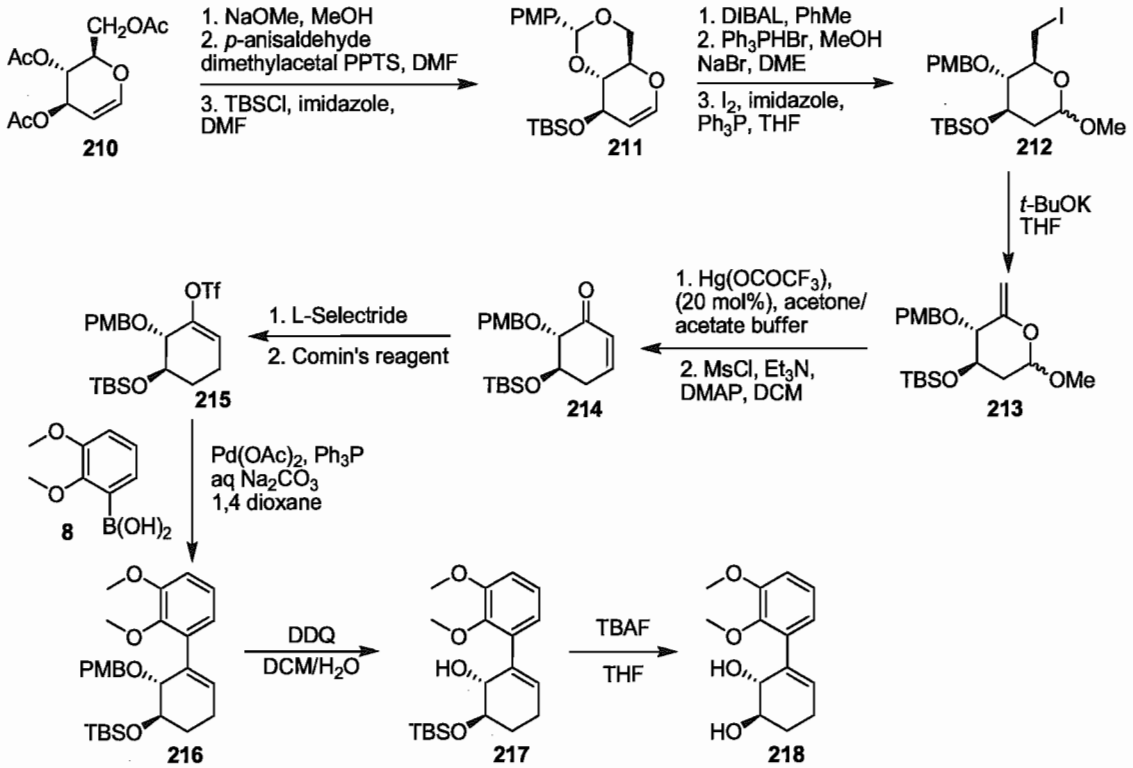



**Figure 52**-Chida's synthesis of intermediate **218**

A cascade Claisen rearrangement was used to set the stereochemistry at both C-13 and C-14. The cascade rearrangement proceeded in 36 % yield. A sequential rearrangement from **217** was also explored.

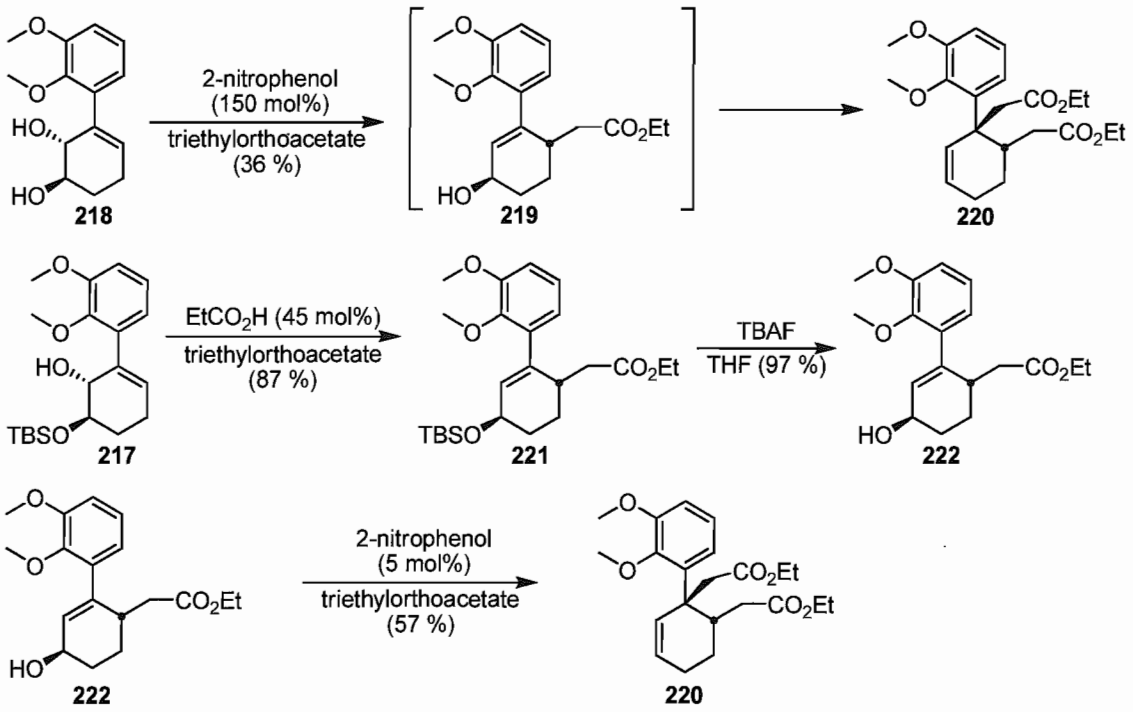



**Figure 53**-Chida's cascade and sequential Johnson-Claisen rearrangements[74]

Following the Claisen rearrangement, the furan ring was completed by epoxidation of the olefin and subsequent intramolecular nucleophilic opening of the epoxide. Protection of the alcohol followed by reduction of the ethyl esters gave a dialdehyde. Friedel-Crafts closure of the B-ring followed by dehydration gave a mixture of **224a-b**. The mixture was subjected to silylation conditions to give **224a**. A reductive amination sequence gave (-)-dihydroisocodeine (**227**). Spectroscopic data for tosylamide **226** and dihydroisocodeine was matched to that reported by Parker.[69]

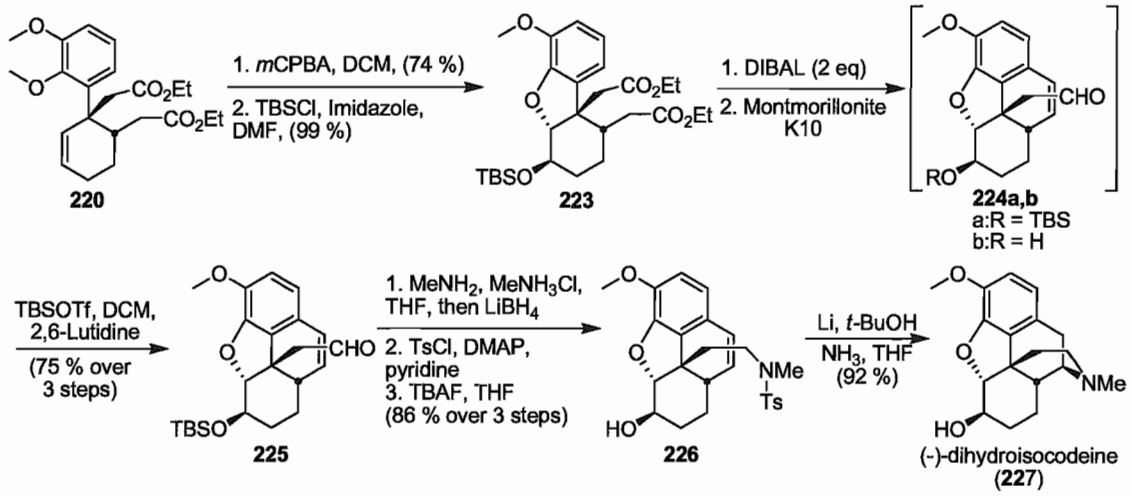



**Figure 54**-Final steps in Chida's formal synthesis of morphine[74]

## 2.3 Microbial Oxidation of Arenes

### 2.3.1 History of microbial oxidation of arenes

The metabolism of arenes by soil bacteria was first reported by Störmer in 1908. In 1968, Gibson and co-workers reported that a strain of *Pseudomonas putida* grew on toluene as its sole carbon source.[76-77] Cell extracts from this organism oxidized benzene, toluene and ethyl benzene at equal rates. Propylbenzene and butylbenzene were metabolized slowly while benzenes with larger substituents (pentyl, heptyl, octyl) were not oxidized. Cell extracts were incubated with proposed intermediates for the degradation of benzene. Phenol and *trans*-dihydrobenzene glycol were metabolized at a much slower rate than catechol and *cis*-dihydrobenzeneglycol. When cell extracts were incubated in the presence of benzene (**228**), catechol (**231**), and *cis*-dihydrobenzene glycol (**230**), catechol was observed to be the only product. This led Gibson to propose the mechanism shown in Figure 55 for the oxidation of benzene to catechol.

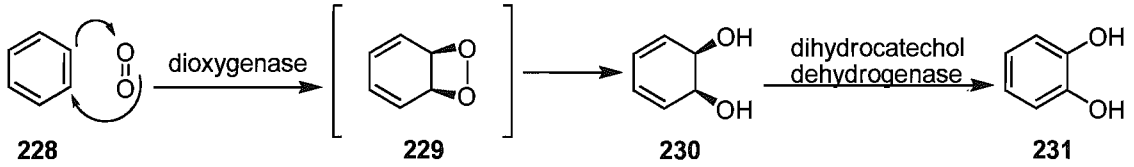
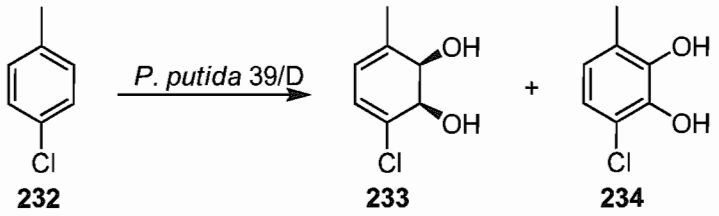



**Figure 55**-Gibson's proposed mechanism for diol and catechol formation by *P. putida* [76]

Incubation of *P. putida* with *p*-chlorotoluene (**232**) yielded two metabolites (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**233**) and 4-chloro-2,3-dihydroxy-1-methylbenzene (**234**),[77] providing further evidence of a *cis*-dihydrodiol intermediate in the metabolism of aromatic substrates (Figure 56).

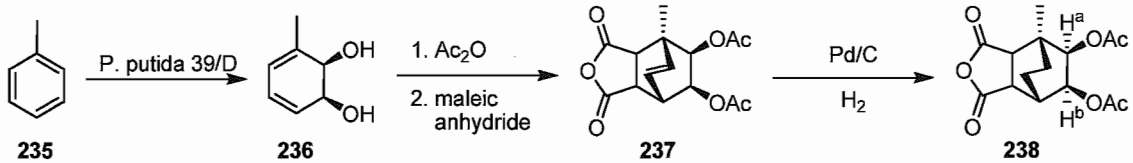



**232** **233** **234**

**Figure 56-**Metabolism of *p*-chlorotoluene by *P. putida*[77]

$^{18}O$ labeled oxygen was used to confirm that the hydroxyl groups of the catechols originated in molecular oxygen.[78] A mutant strain of *P. putida* was isolated that did not have the requisite enzymes to process *cis*-cyclohexadiene diols.[79] This allowed for the isolation of several diols in sufficient quantity for stereochemical proof.

Gibson was able to isolate *(+)-cis*-2,3-dihydroxy-1-methyl-4,6-cyclohexadiene (**236**) produced by the action of the enzyme toluene dioxygenase and confirmed the relative stereochemistry was indeed *cis*.[79] Determination of a *cis* relationship between the hydroxyl groups could not be established by NMR analysis of the free diol. In order to get a clearer picture of the relationship of the two hydroxyl groups, a more rigid structure was needed.[79] Diol **236** was protected as a diacetate and condensed with maleic anhydride. The resulting Diels-Alder adduct **237** was then hydrogenated and the fully saturated tricycle **238** was analyzed by NMR spectroscopy to prove the *cis* relationship (Figure 57). The relative and absolute stereochemistry were later confirmed by X-ray diffraction.[80]




**235** **236** **237** **238**

**Figure 57-**Proof of relative stereochemistry of *P. putida* metabolites[79]

Proof of the absolute stereochemistry of **236** was published by Gibson in 1973.[81] Hydrogenation of the diol yielded diastereomeric diols **239a-b** that were separable as

their monobenzoates. Diol **239b** was then oxidized with Jones reagent to (-)-2-(R)-adipic acid (**240**) which proved the absolute stereochemistry was 1*S*,2*R* (Figure 58).

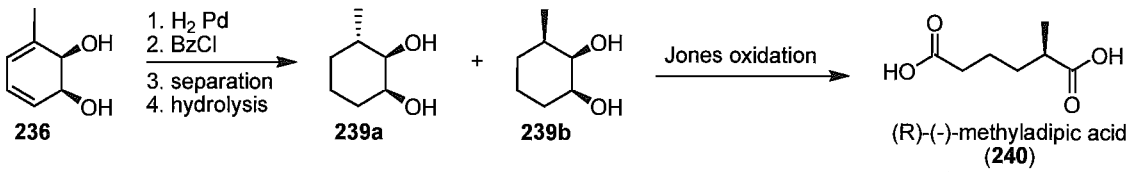



**Figure 58**-Proof of absolute stereochemistry of *P. putida* metabolite **236**[81]

### 2.3.2 Isolation and characterization of toluene dioxygenase (TDO)

In 1977, Gibson was able to isolate the enzyme responsible for the oxidation of aromatic compounds to *cis*-diene diols. He named this enzyme toluene dioxygenase or TDO.[82] TDO was discovered to be a three component enzyme composed of a flavoprotein and two non-heme iron containing proteins. These proteins required electrons from NADH. Further study led to a reliable purification method.[83]

Through the study of mutant strains of *P. putida*, Gibson and Zylstra were able to determine the nucleotide sequence of the genes encoding TDO.[84] The genes were then expressed in a strain of *E. coli* JM109(pDTG601). The use of *E. coli* for biotransformations of aromatic compounds has many advantages over mutant *P. putida* strains. *E. coli* has been studied very thoroughly and its growth conditions have been well optimized. *P. putida* requires an aromatic inducer to express TDO, usually toluene or chlorobenzene. Because the inducer is also a substrate, it must be separated from the metabolite. The recombinant organism, however, uses β-isopropylthiogalactopyranoside (IPTG) as an inducer. The plasmid incorporated into *E. coli* also contains multiple copies of the genes responsible for TDO allowing much greater expression and thus higher yields of diols.

### 2.3.3 Substrate scope and specificity

Dihydroxylations by TDO have been found to occur in a fairly predictable manner with respect to regio-, stereo-, and enantioselectivity. After screening a number of 1,4-disubstituted benzenes, Boyd developed a model to account for and predict the regio- and stereoselectivity of TDO oxidations.[85] According to Boyd's model, dihydroxylations proceed as shown in Figure 59. When the difference in relative size between the two substituents (S and L) is greater, the diol is obtained in higher er.

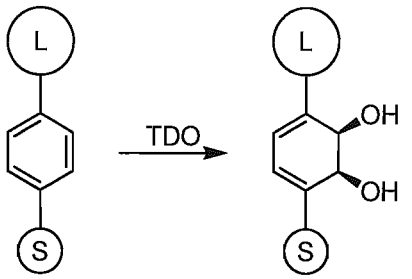



**Figure 59**-Boyd's model for the prediction of stereoselectivity of TDO dihydroxylations[85]

Boyd later expanded his model to include larger, more conformationally flexible substituents [86-87] and determined the absolute stereochemistry of the metabolites reported in his 1993 publication.[88] Boyd's model has also proven to be fairly accurate at prediction the regio- and stereochemistry of *ortho-* and *meta-* as well as *para-* substitution on benzene rings (Figure 60).[89]

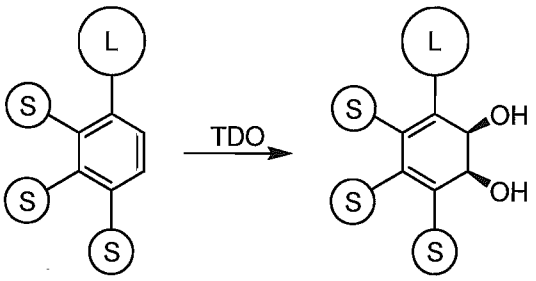



**Figure 60**-Boyd's expanded model for the stereoselectivity of TDO dihydroxylations[89]

Benzenes substituted with charged or very polar functional groups are often not metabolized.[89] These substituents include phenols, sulfoxides and sulfones, carboxylic acids and amines. When these substrates are metabolized it is usually through pathways other than TDO. Nitrobenzene was originally thought to be among the substrates not metabolized by TDO but was later shown to be metabolized to a diol which was then degraded by other enzymes present in the bacterial cells.[90-91]

An ongoing component of the research program in the Hudlicky group is the isolation and structural determination of new metabolites of TDO. In 1992, Hudlicky and co-workers isolated several metabolites derived from *ortho*-chlorostyrene (**241**).[92] This was followed a year later by a similar study on *ortho*-bromostyrene (**242**).[93] Oxidation of these substrates led to mixtures of products, as shown in Figure 61.

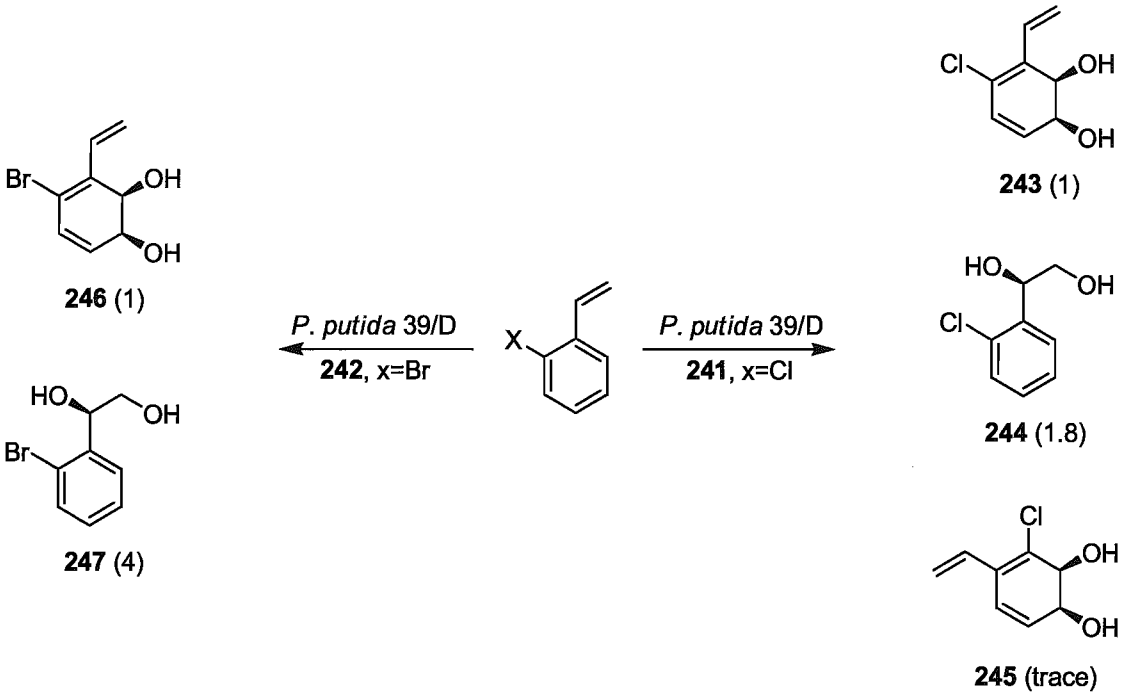
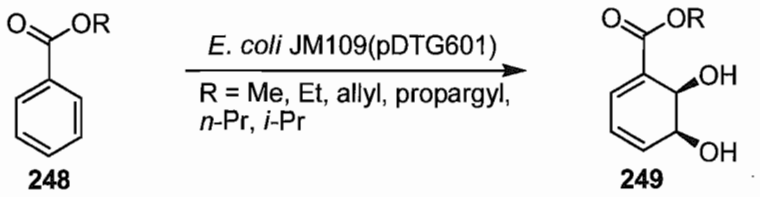



**Figure 61**-Oxidation of *o*-halostyrenes by TDO (ratio)[92-93]

Recently, Hudlicky and co-workers tested several benzoate esters **248** as possible substrates of TDO.[94] Methyl, ethyl, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu, allyl, and propargyl benzoate

esters were tested as substrates to determine the role of steric bulk in oxidation by TDO. Methyl, ethyl, allyl and propargyl benzoate were all metabolized and their corresponding diols were isolated in approximately 1 g/L yield. The diols resulting from the oxidation of *n*-Pr and *i*-Pr benzoate were isolated in trace amounts. *n*-Bu and *t*-Bu benzoate were not metabolized.



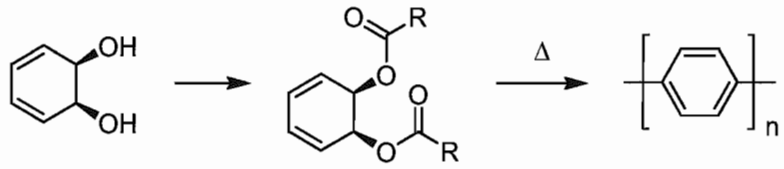

**248** **249**

**Figure 62**-Metabolism of benzoate esters by TDO[94]

### 2.3.4 Use of microbial oxidation in synthesis

There are over 400 known metabolites of TDO, however, relatively few have been exploited in synthesis. The majority of TDO metabolites used in synthesis are the diols derived from benzene, toluene and monosubstituted halobenzenes.[95]

The first use of *cis*-dihydrodiols was a preparation of polyphenylene (**251**) reported by researchers at Imperial Chemical Industries (ICI) in 1983.[96] Diol **230** was derivatized as a carbamate or ester **250** and then heated to initialize the formation of polyphenylene (Figure 63).




**230** **250** **251**
R = OMe, Me, Ph

**Figure 63**-Preparation of polyphenylene from **230**

The first application of a TDO metabilite in natural product synthesis was reported by Ley and co-workers in the racemic synthesis of (±)-pinitol (**255**) in 1987

(Figure 64).[97] Ley's synthesis began with diol **230** which was protected as its benzoate **252**. Treatment with *m*CPBA gave a diastereomeric mixture of epoxides **253a-b** in 14 % and 73 % respectively. Epoxide **253b** was opened with methanol in camphorsulfonic acid (CSA) to give **254** in 88 % yield. Dihydroxylation with osmium tetroxide followed by deprotection gave (±)-pinitol.

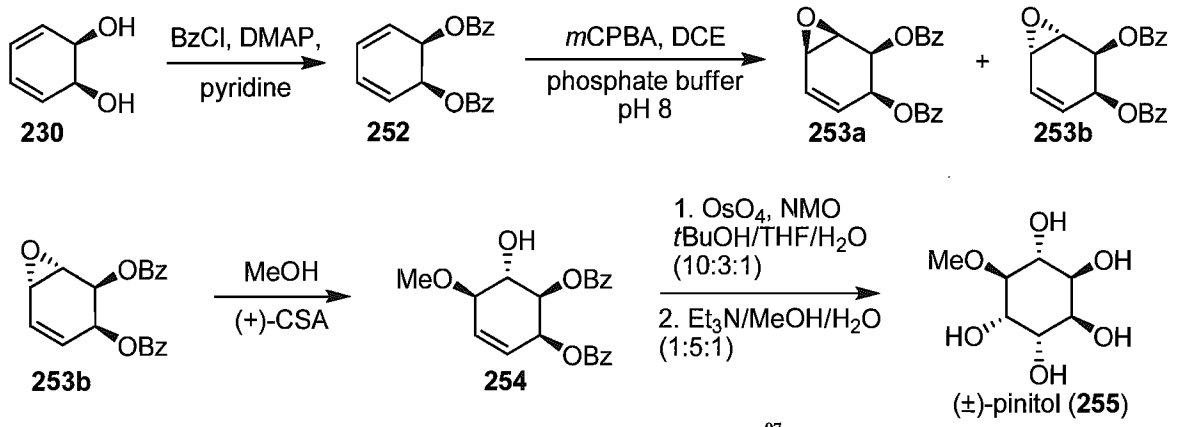



**Figure 64**-Ley's synthesis of (±) pinitol[97]

The first use of diols by the Hudlicky group involved the preparation of prostaglandin synthon **259** in 1989.[98] This synthesis was the first example of an enantioselective synthesis using diols (Figure 65). The diol resulting from the oxidation of toluene was protected as its acetonide **256** and then subjected to ozonolysis. Hemiacetal **257** was then carefully dehydrated on neutral alumina to **258** which can be transformed to prostaglandin $E_{2\alpha}$ **260** by the method of Johnson and Penning.[99]

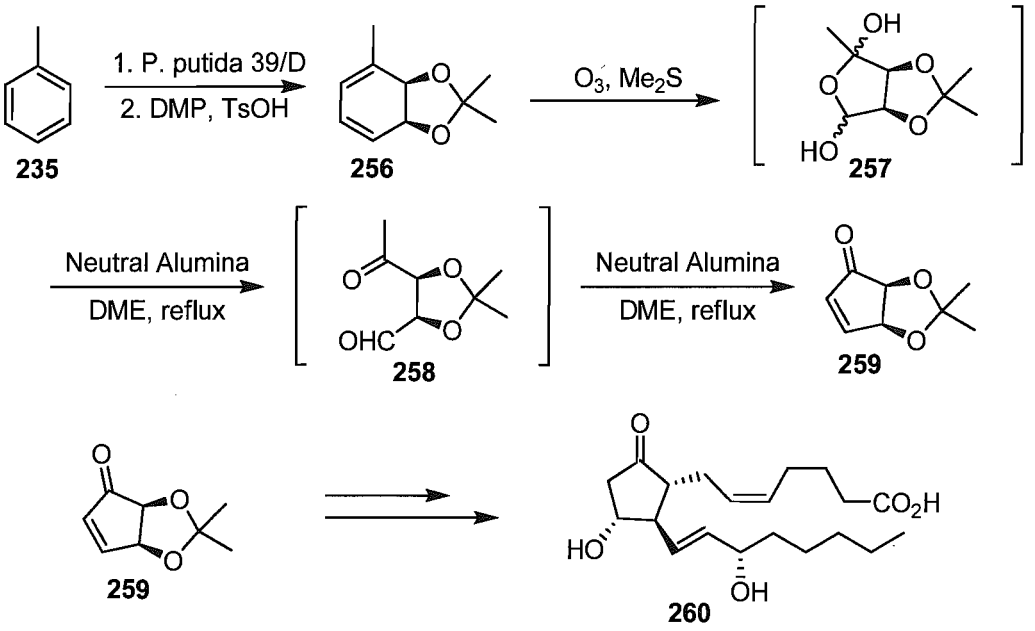



**Figure 65**-Hudlicky's synthesis of prostaglandin synthon **259**[98]

Hudlicky and co-workers have shown that diols are extremely useful starting materials in the synthesis of terpenes[100-101], sugars [102-103], pseudosugars, [104] cyclitols [105], aza-sugars [106], sphingosines [107-108], and alkaloids of the pyrrolizidine[109], amaryllidaceae[110-118], and morphine[67,119-120] families.

Several landmark syntheses, including syntheses of conduritols[121], Amaryllidaceae alkaloids[110-111,113], heliotridanes[109], and triquinanes[122], are shown in Figure 66. Several recent reviews contain more exhaustive lists of syntheses employing microbial dihydroxylation.[89,95,123-125]

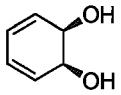
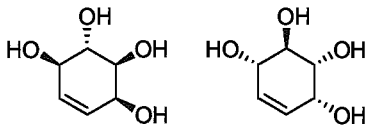
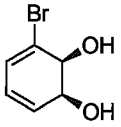
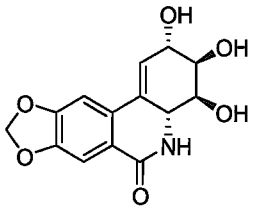
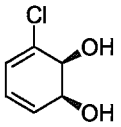
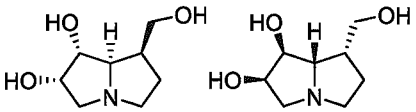
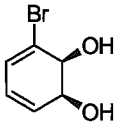
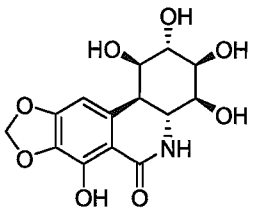
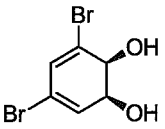
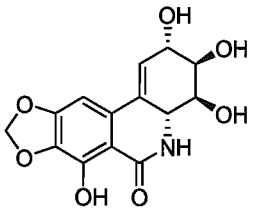
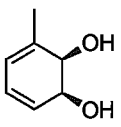
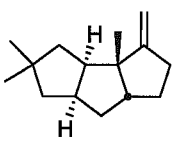
| Starting material | Product | Author (year) | Reference number |
|---|---|---|---|
|  **230** |  (+)- and (-)-conduritol F (**263**) | Ley (1990) | 121 |
|  **12** |  lycoricidine (**264**) | Hudlicky (1992) | 110 |
|  **261** |  (+)- and (-)-trihydroxyheliotridane (**265**) | Hudlicky (1990) | 109 |
|  **12** |  pancratistatin (**266**) | Hudlicky (1995) | 111 |
|  **262** |  narciclasine (**267**) | Hudlicky (1999) | 113 |
|  **236** |  (-)-hirsutene (**268**) | Banwell (2004) | 122 |

**Figure 66**-Landmark syntheses employing microbial dihydroxylation[95]

## 2.4 Claisen rearrangement

In 1912, Ludwig Claisen reported a [3,3] sigmatropic rearrangement of allyl vinyl ethers or their nitrogen or sulfur analogs **269**.[126] In his seminal disclosure, Claisen described the transformation of phenyl allyl ether (**271**) to 2-allylphenol (**273**) and the transformation of *O*-allylated acetoacetate (**274**) to its *C*-allyl isomer **275** (Figure 67). The Claisen rearrangement quickly became a widely used reaction in organic synthesis.

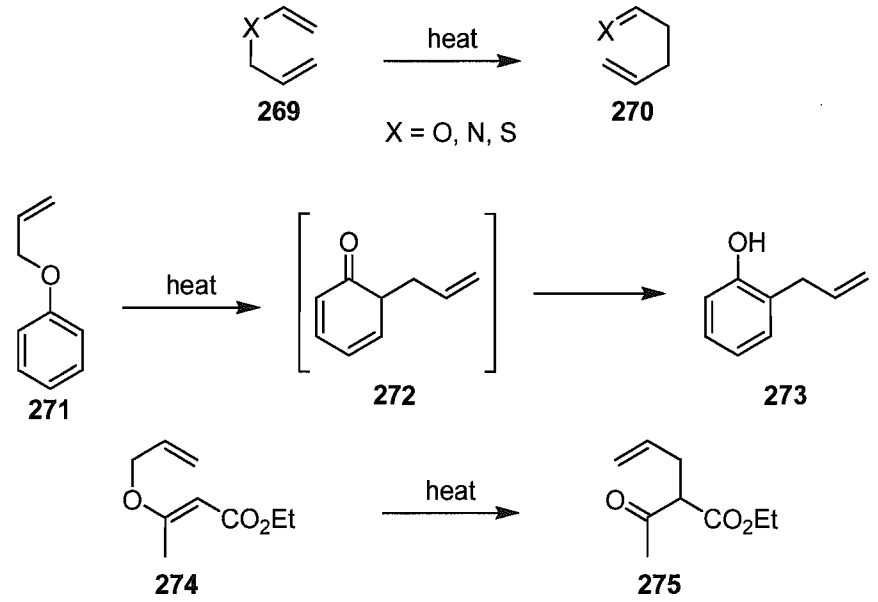



**Figure 67**-The Claisen rearrangement

The Claisen rearrangement is generally thought to proceed through a chair- or boat-like transition state (**277** or **279** respectively) (Figure 68).[127] Early kinetic studies of the Claisen rearrangement of allyl vinyl ether (**276**), the simplest structure that can undergo Claisen rearrangement, were performed by Schuler who found the kinetics to be first order and the energy of activation to be 30.6 kcal/mol.[128] Since the rearrangement is highly exothermic, the Hammond-Leffler postulate[129-130] predicts that the transition state is closer in character to the starting material than the product.[131] Gajewski and McMichael published kinetic isotope studies back to back and both determined that the

transition state had a certain amount of radical character.[131-132] However, there is still some disagreement on the exact nature of the transition state.[133]

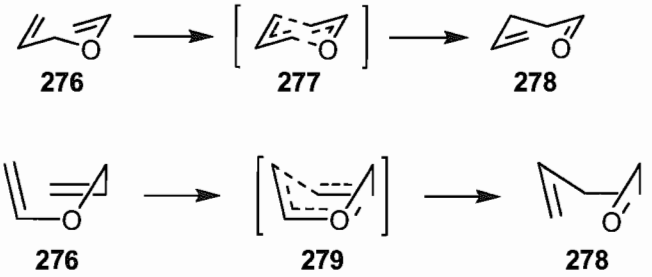



**Figure 68**-Chair and boat transition states for the Claisen rearrangement

### 2.4.1 Variations of the Claisen rearrangement

In the ninety-eight years since the discovery of the Claisen rearrangement there has been many variations of the rearrangement published. Martin Castro provided an excellent overview of the variations of the Claisen rearrangement in her 2004 review.[134]

In 1973, Baldwin reported the Claisen rearrangements of zinc enolates **281** dubbed the Reformatskii-Claisen rearrangement.[135] The Reformatskii-Claisen rearrangement proceeds under neutral conditions. Lang reported a variation of the Reformatskii-Claisen rearrangement of chlorodifluoroacetates **283** in the presence of chlorotrimethylsilane (Figure 69).[136]

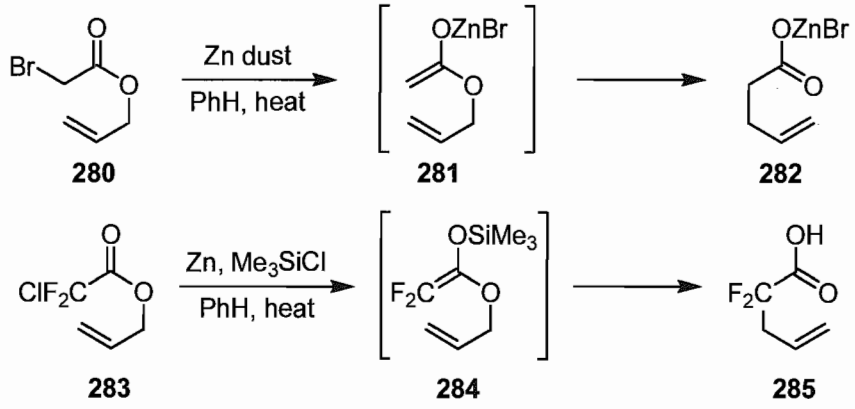



**Figure 69**-The Reformatskii-Claisen rearrangement[135-136]

Because of the greater thermodynamic stability of the C-O double bond relative to the C-C double bond, Claisen rearrangements are usually irreversible. However, retro-Claisen rearrangements can occur if the reaction reduces strain in the molecule. Boeckman showed that bridged bicyclic systems **286** will undergo retro-Claisen rearrangements to reduce torsional strain at the bridgehead[137] and Rhoads performed retro-Claisen rearrangements on vinylcyclopropane carboxaldehydes **288** (Figure 70).[138] While Rhoads referred to the conversion of **288** to **289** a retro-Claisen rearrangement, it is really an oxodivinyl Cope rearrangement.

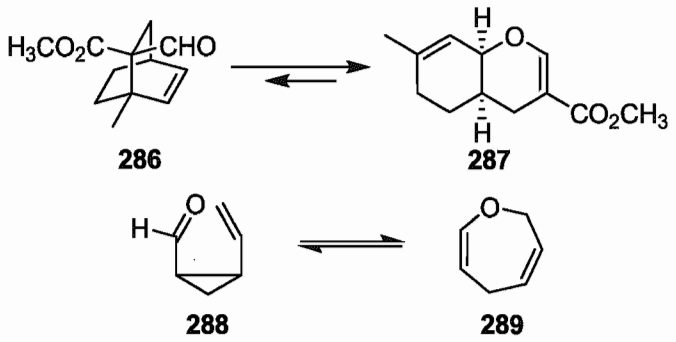



**Figure 70**-The retro-Claisen rearrangement[137-138]

In 1972, Ireland reported the Claisen rearrangement of the lithium enolates of allyl esters **291** and the trimethylsilyl enolates of allyl esters **293** (Figure 71).[139] These reactions proceeded at low temperatures and often without the formation of side products. Stereoselective enolate formation can be employed to control the stereochemistry of Ireland-Claisen rearrangements.[140]

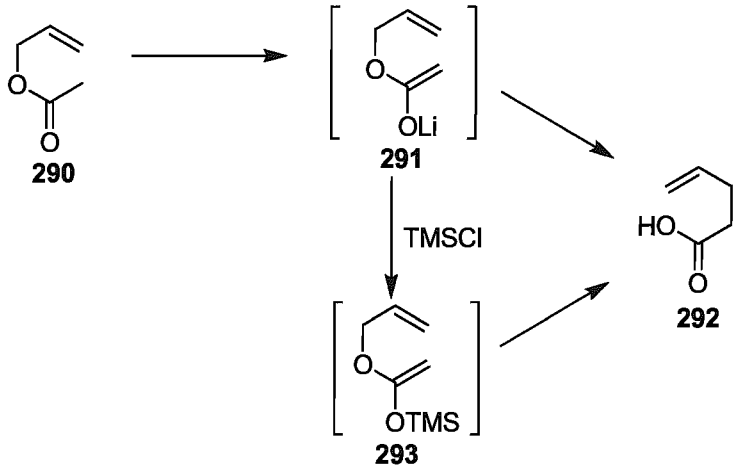



**Figure 71**-The Ireland-Claisen rearrangement

In 1994, Uli Kazmaier reported a variation of the Ireland-Claisen rearrangement (often referred to as the Kazmaier-Claisen rearrangement) that used a metal to chelate the enolate formed by the deprotonation of an ester (Figure 72).[141-142] This method was applied to the synthesis of several unnatural amino acids of type **297**. The Kazmaier-Claisen rearrangement proceeds through a boat-like transition state **295** rather than a chair-like transition state **296** and is often highly diastereoselective.[142] The use of a chelating agent allows for reactions at higher temperatures than Ireland-Claisen rearrangements as the chelated enolates are much more stable than lithium enolates.

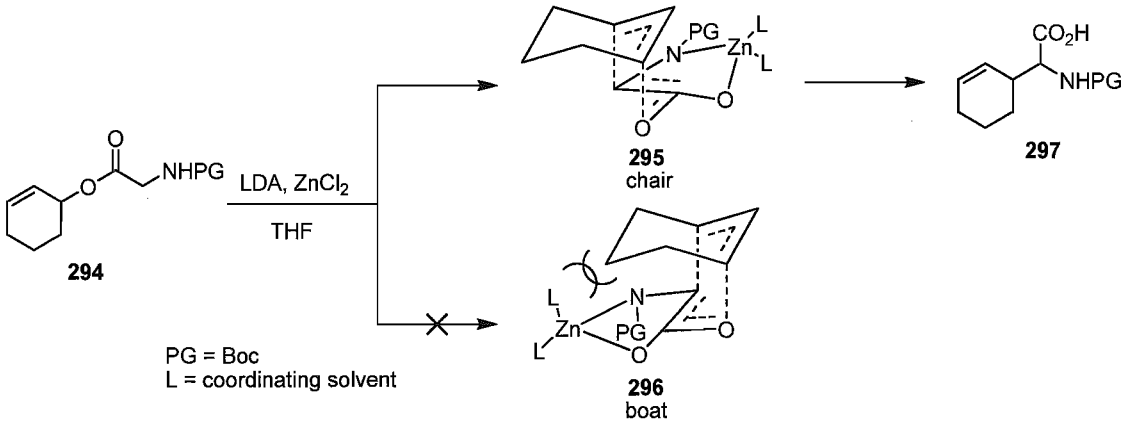



**Figure 72**-The Kazmaier-Claisen rearrangement

Johnson described the Claisen rearrangement of allylic alcohols in an excess of triethyl orthoacetate (**298**) and a catalytic amount of acid, usually propionic acid.[143] Under acidic conditions, triethyl orthoacetate loses ethanol to form ketene diethyl acetal (**299**). An allylic alcohol **300** adds to ketene diethyl acetal and then undergoes another loss of ethanol to generate a mixed ketene acetal **302**. The mixed acetal then rapidly undergoes a [3,3] sigmatropic rearrangement (Figure 73). The Johnson-Claisen rearrangement is advantageous because only one operation is required as opposed to vinyl ether formation followed by pyrolysis. Daub reported Johnson-Claisen rearrangements with trimethyl orthoacetate.[144] McGeary and Cosgrove developed a method of generating mixed orthoesters and and a triisobutylaluminum catalyzed Johnson-Claisen rearrangement that proceeds at room temperature.[145-146]

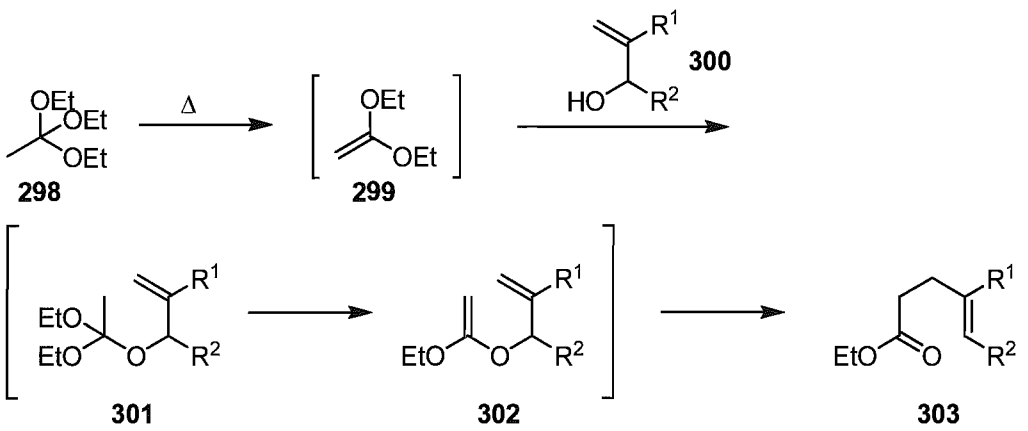



**Figure 73**-The Johnson-Claisen rearrangement[143]

There have been several other variations of the Claisen rearrangement published including chiral auxiliary and catalytic reactions. Variants of the Claisen rearrangement not covered here and several syntheses employing Claisen rearrangements are covered in Martin Castro's review.[134]

### 2.4.2 Use of the Claisen rearrangement in organic synthesis

The Claisen rearrangement has also been featured in the synthesis of many complex natural products including Ireland's synthesis of lasalocid A[147], Paquette's synthesis of basmane diterpenes[148], Kim's synthesis of pancratistatin[149] and Mioskowski's synthesis of halomon.[150]

The Claisen rearrangement has been used extensively by the Hudlicky group. A Johnson-Claisen rearrangement is featured in Hudlicky's general method for the preparation of linear and non-linear triquinanes (Figure 74).[151] In the synthesis of linear triquinanes **307a**, a vinyl unit is added to the carbonyl of **304** and the Johnson-Claisen rearrangement takes place on the less substituted olefin to give (**306a**). To synthesize non-linear triquinanes **307b**, an alkynyl unit is added to the carbonyl of **304** and the cyclic olefin participates in the rearrangement to give **306b**.

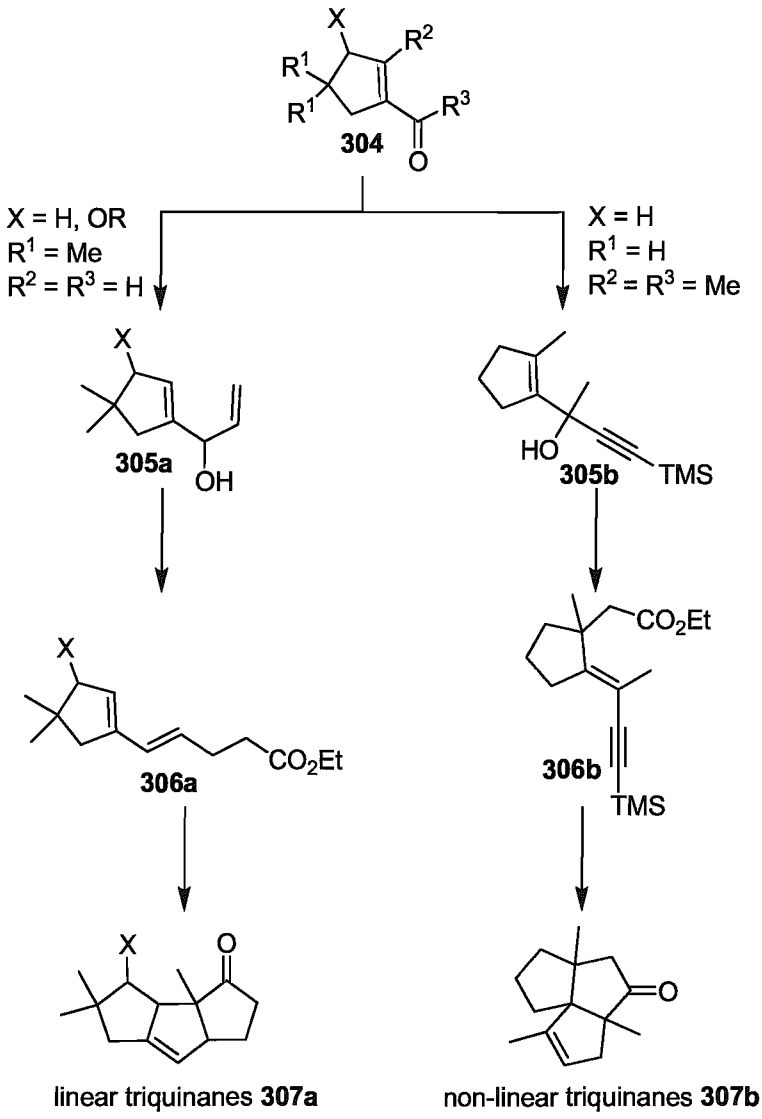



**Figure 74**-Hudlicky's general method for the synthesis of linear and non-linear triquinanes[151]

In 1997, Hudlicky reported the synthesis of several unnatural amino acids **310a-d**, and **311a-d**.[152] The key step of the synthesis was a Kazmaier-Claisen rearrangement of **309a-d** to **310a-d** and **311a-d** (Figure 75). This sequence is the basis for our synthesis of the C-ring of morphine (**3**) described in this thesis.

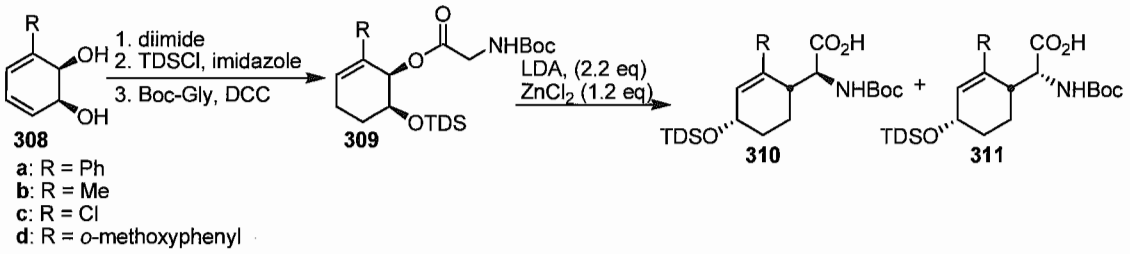



**Figure 75**-Hudlicky's preparation of unnatural amino acids via a Kazmaier-Claisen rearrangement

Chida's synthesis of morphine (**3**), described in section 2.2.2 employed a cascade Johnson-Claisen rearrangement as the key step that set the stereochemistry at the C-13 quaternary center and at C-14. The cascade Claisen rearrangement of **218** to **220** proceeded in 36 %. A stepwise procedure starting from protected diol **217** gave the rearranged product in 48 % yield over three steps (Figure 76).

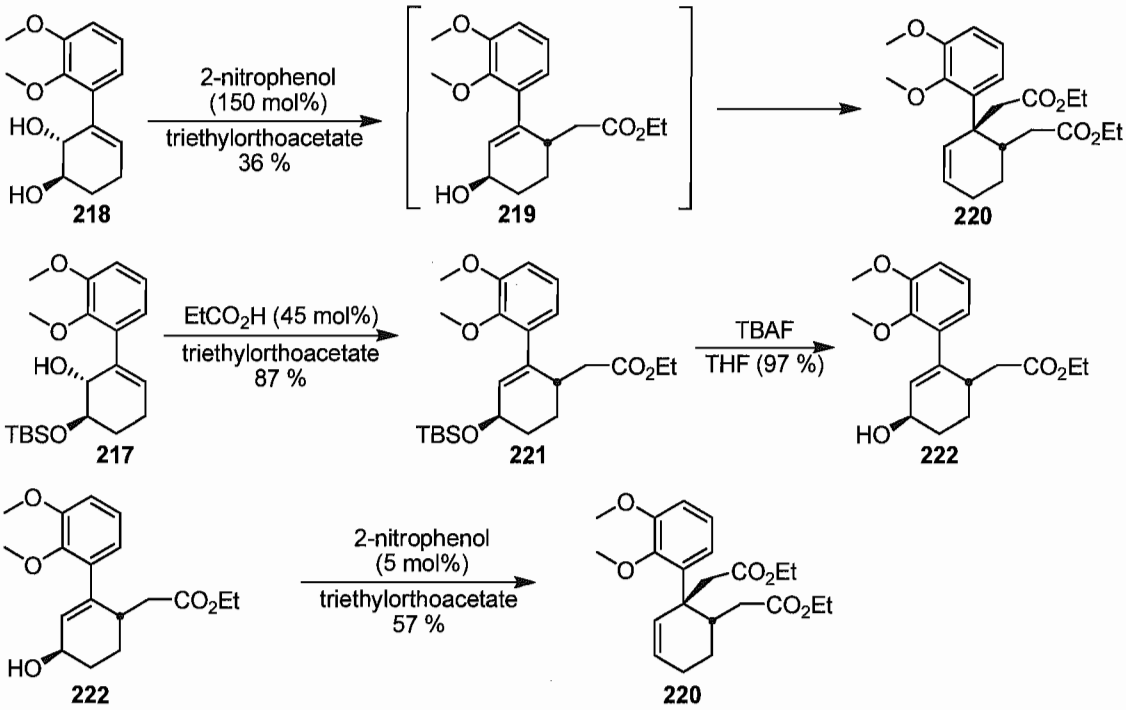



**Figure 76**-Chida's cascade and sequential Johnson-Claisen rearrangements

## 3. Discussion

### 3.1 Introduction

The first part of the present studies describes the efforts to develop a thermally stable version of the Burgess reagent that retains the reactivity of the original reagent. Such a reagent would be useful to synthetic chemists who are employing the Burgess reagent in reactions at elevated temperatures. At high temperatures, the original Burgess reagent is unstable and its decomposition leads to reduced yields. A more stable reagent would also require less care in handling and could be stored for longer periods of time.

The second part of this thesis details the progress toward the total synthesis of morphine beginning with the enzymatic dihydroxylation of bromobenzene. As pointed out in the Historical Section, the ultimate goal of our synthetic studies of morphine is to develop a route efficient enough to compete with isolation of morphine from natural sources. Progress toward this goal is discussed herein.

In addition, the characterization of several new metabolites of toluene dioxygenase provides new chiral materials that can be utilized in total synthesis by academic and industrial chemists. The characterization of new metabolites helps us to better understand the nature of toluene dioxygenase and its strengths and limitations. Hopefully, more chemists will realize the environmental benefits of enzymatic reactions and be encouraged to incorporate enzymatic reactions into their total synthesis efforts.

### 3.2 New Burgess reagents

Three new Burgess reagents were synthesized for this study. Also included were the original Burgess reagent (**1**) and the menthyl chiral auxiliary Burgess reagent **124** (Figure 77). The goal was to stabilize the negative and positive charges with electron withdrawing and donating groups respectively as shown in Figure 1 (page 1). For the electron withdrawing group, we chose trifluoroethanol and for the electron donating group we replaced triethylamine with *N*-methyl piperidine. Although **1** is commercially available from Sigma-Aldrich, the commercial reagent is expensive and often contains impurities.[13] The Burgess reagent was prepared as described in Burgess' Organic Syntheses paper.[153] Menthyl Burgess reagent **124** was prepared by the method described by Hudlicky.[22]

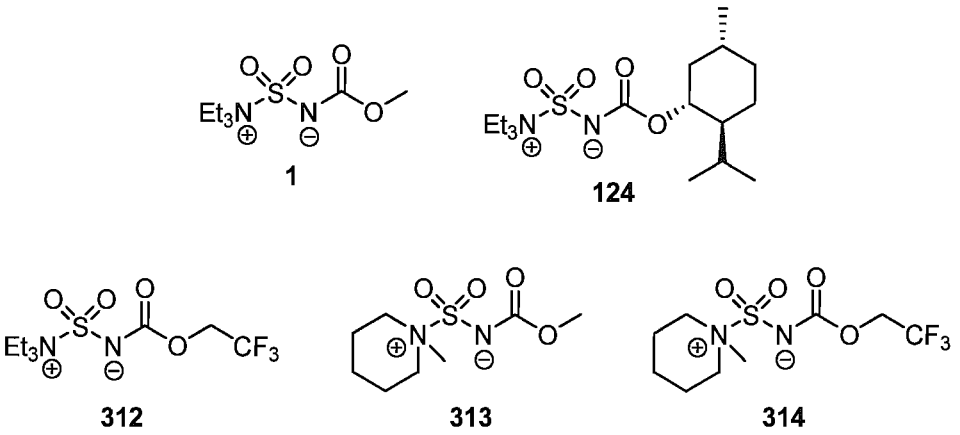



**Figure 77**-Burgess reagents employed in this study

Reagent **313** was prepared by Burgess' method with the substitution of triethylamine with *N*-methylpiperidine. Fluorinated reagents **312** and **314** required more modification of Burgess' procedure to synthesize. Chlorosulfonyl isocyanate (**117**) was treated with 2,2,2-trifluoroethanol in benzene to give carbamate **316**. Carbamate **316** proved to have very limited solubility in benzene, therefore, the solvent was switched to

THF. Treatment of **316** with 2.2 equivalents of triethylamine yielded reagent **312** and treatment of **316** with *N*-methylpiperidine gave **314** (Figure 78).

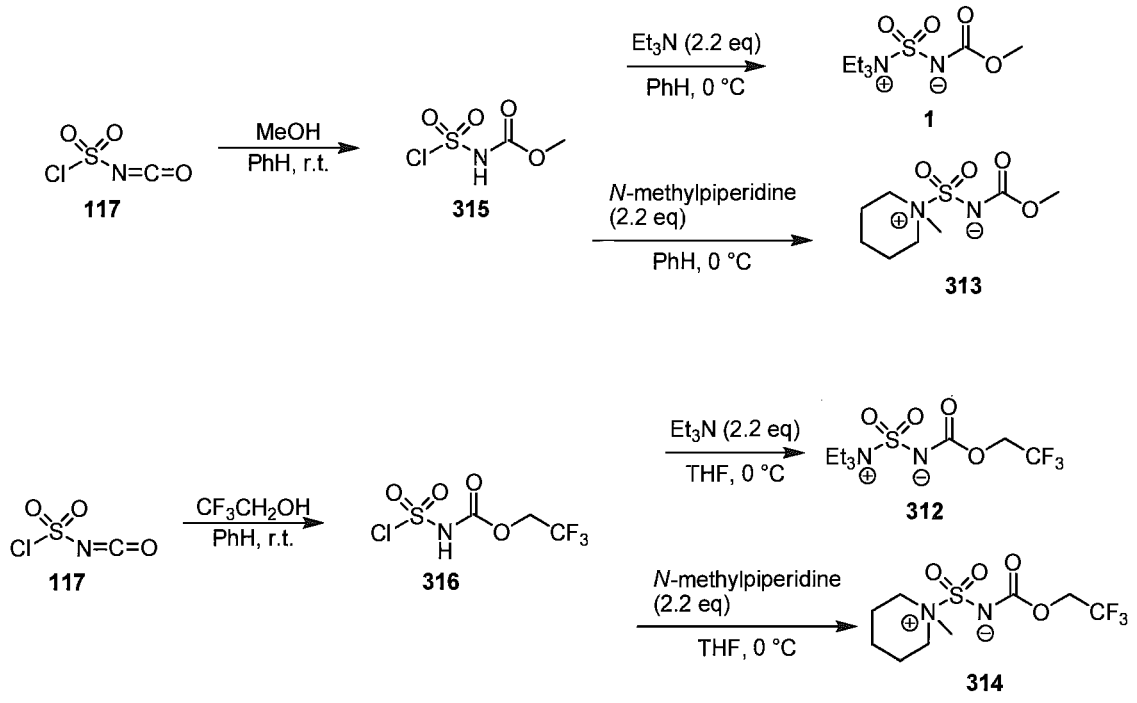
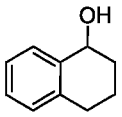
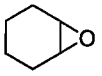
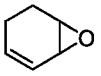
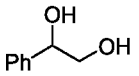
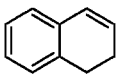
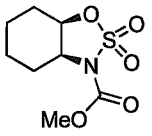
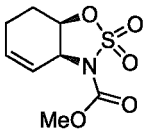
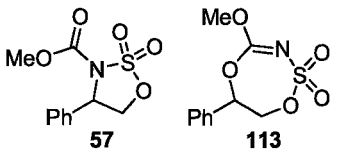
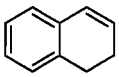
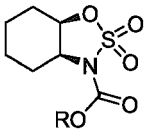
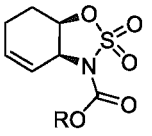
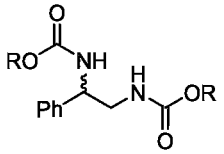
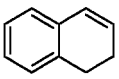
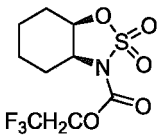
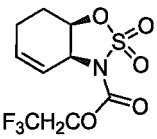
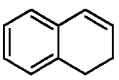
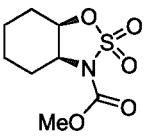
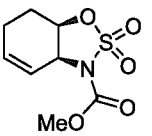
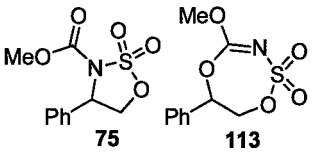
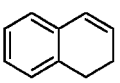
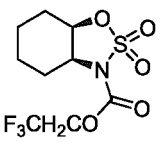
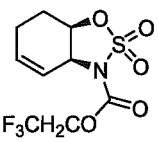



**Figure 78**-Preparation of Burgess reagents

The reactivity of the new Burgess reagents was compared to the original Burgess reagent and the menthyl reagent **124** in a series of reactions.[154] The results are shown in Table 1. Each reagent was tested in a dehydration reaction, reactions with epoxides, and with styrene diol. Yields of the dehydration of **317** to **318** were about 30 % higher when the new Burgess reagents were employed. In the reaction with cyclohexene oxide (**104**) the *N*-methylpiperidine reagent gave a 16 % improvement in yield over that observed with the original reagent **1**. The fluorinated reagents however, gave a significant decrease in yield. We believe that this is because the nitrogen atom bearing the negative charge is too stable and not nucleophilic enough to open the epoxide. When the more activated allylic epoxide **152** was treated with our Burgess reagents we did see higher yields of sulfamidates compared to the opening of **104**. The fluorinated reagents **312** and **314** were

nucleophilic enough to open epoxide **152** and gave sulfamidate **324** in modest yield. In the reaction of reagents **1** and **313** we obtained yields similar to those reported by Nicolaou.[13-14] Reagents **312** and **314** gave only sulfonation of the alcohol, which is consistent with the mechanism for the formation of sulfamidates from diols proposed by Nicolaou.[13-14] The formation of dicarbamate **322** was quite surprising. However this can also be rationalized by invoking a bis-sulfonated intermediate **325**, which, for steric reasons, may not undergo intramolecular displacement at the benzylic position. A less sterically demanding intramolecular displacement may take place yielding sulfamidate **326**, which then could be substituted at the benzylic position by the carbamate anion **327**, created by the displacement of the second equivalent of **124**. Another option is an intramolecular $S_N2$ type reaction similar to the mechanism described by Burgess for the formation of carbamates from primary alcohols (Figure 79).[3]

**Table 1**-Reactivity trends of the new Burgess reagents in dehydration, reactions with oxiranes, and with styrene diol

| Starting material |  **317** |  **104** |  **152** |  **74** |
|---|---|---|---|---|
| Reagent | Product(s) | | | |
| **1** |  |  |  |  |
| | **318** (63 %) | **109** (40 %) | **319** (30 %) | **75**:**107** (77 %) (98:2) |
| **124** |  |  |  |  |
| | **318** (60 %) | **320** (35 %) R=Menthyl | **321** (36 % ) R=Menthyl | **322** (70 %) R=Menthyl |
| **312** |  |  |  | sulfonation only |
| | **318** (93 %) | **323** (12 %) | **324** (53 %) | |
| **313** |  |  |  |  |
| | **318** (94 %) | **109** (56 % ) | **319** (57 %) | **57**:**107** (82 %) (95:5) |
| **314** |  |  |  | sulfonation only |
| | **318** (93 %) | **323** (17 %) | **324** (45 %) | |

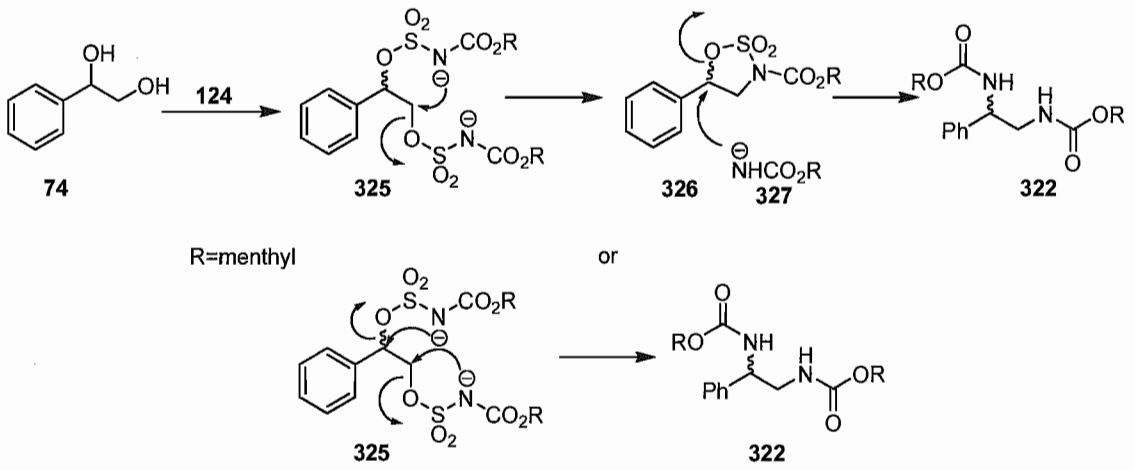



**Figure 79**-Possible mechanisms for the formation of **322**

### 3.3 Stability studies

To determine the thermal stability of the reagents, we chose to follow their decomposition in THF-$d_8$ at 50 °C and at reflux by monitoring the content of the sample by $^{13}C$ NMR. Originally, we sought to use $^{1}H$ NMR but as the reagent decomposed, there was quite a bit of signal broadening and the signals arising from the decomposition products often overlapped the reagent signals. A timed series of $^{13}C$ NMR spectra were recorded for each reagent. For each spectrum the peak area of the carbamate $^{13}C$ signal (around 157 ppm) was determined by direct integration and calibration against solvent $^{13}C$ signal corresponding to THF-$d_8$ at 64.6 ppm. The magnitude of the carbamate $^{13}C$ signal in the first spectrum was set at 100%.[154] The results are shown in Figures 80 and 81 and are compared with those obtained for the original Burgess reagent as well as its menthyl chiral auxiliary version. [The plots shown are the actual decays with percent content illustrated on the left.]

As seen in Figure 80, all reagents are stable at 50 °C for several hours. The original Burgess reagent (**1**) and menthyl reagent **124** decompose at the fastest rate and have half-lives of 216 and 198 minutes respectively. The fluorinated reagent **312** shows a

modest increase in stability. The *N*-methylpiperidine reagents **313** and **314** are stable at 50 °C for over 12 hours. At reflux, the half lives of **1** and **124** drop dramatically to 19 and 13 minutes respectively and are undetectable after one hour. Again, reagent **312** shows an increase in stability. The *N*-methylpiperidine reagents **313** and **314** are the most stable and decomposition is negligible for over three hours at reflux in THF (Figure 81).

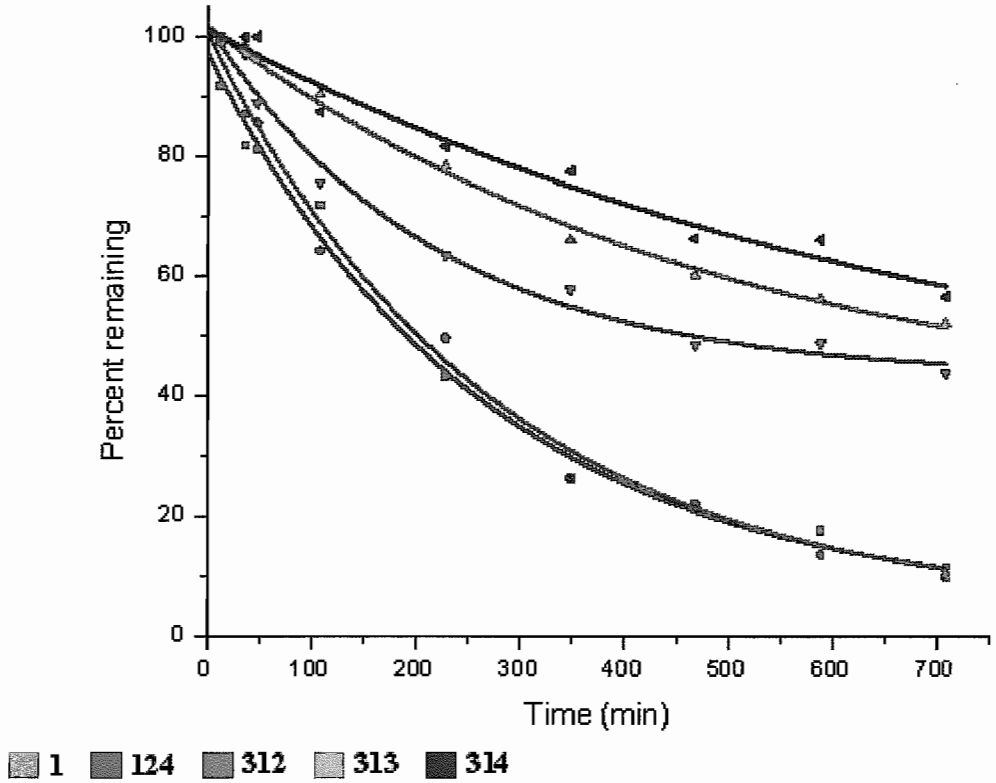



**Figure 80**-Decomposition of Burgess reagents at 50 °C in THF-$d_8$ as a function of time

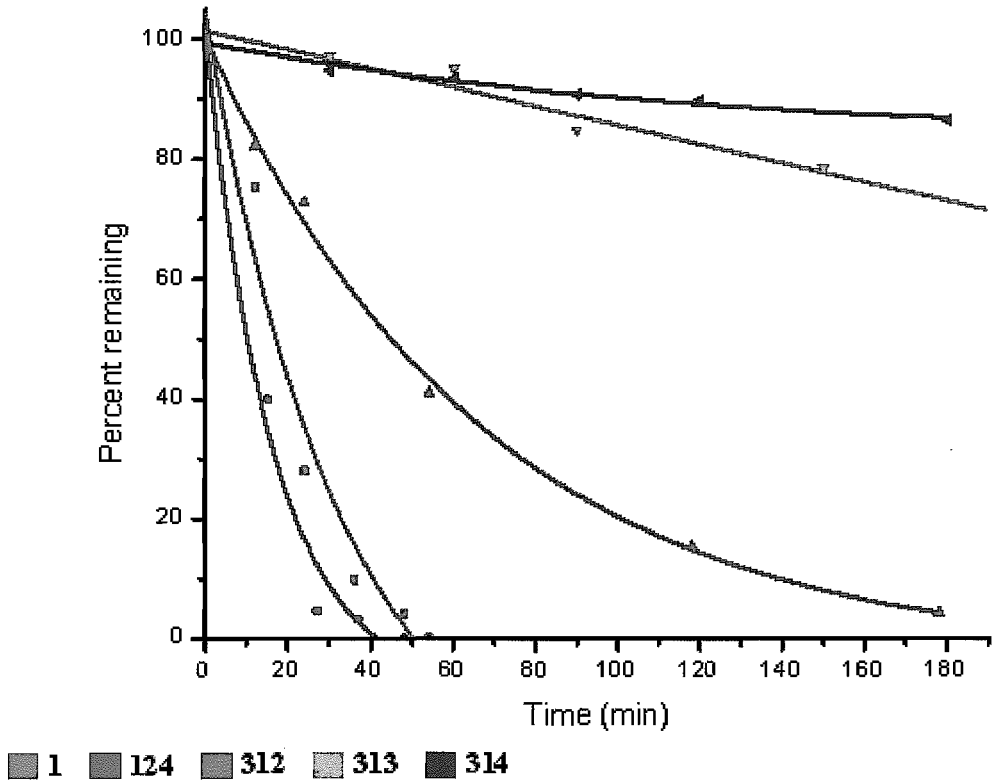



**Figure 81**-Decomposition of Burgess reagents at reflux in THF-$d_8$ as a function of time

Figures 82-86 show the decomposition of each reagent at both 50 °C and at reflux to illustrate the relative rates of decomposition at reflux than at 50 °C. Reagents **1**, **124**, and **312**, decompose much more rapidly at reflux than at 50 °C. The more stable *N*-methyl piperidine reagents **313** and **314**, do not show as much of a decrease in stability at reflux.

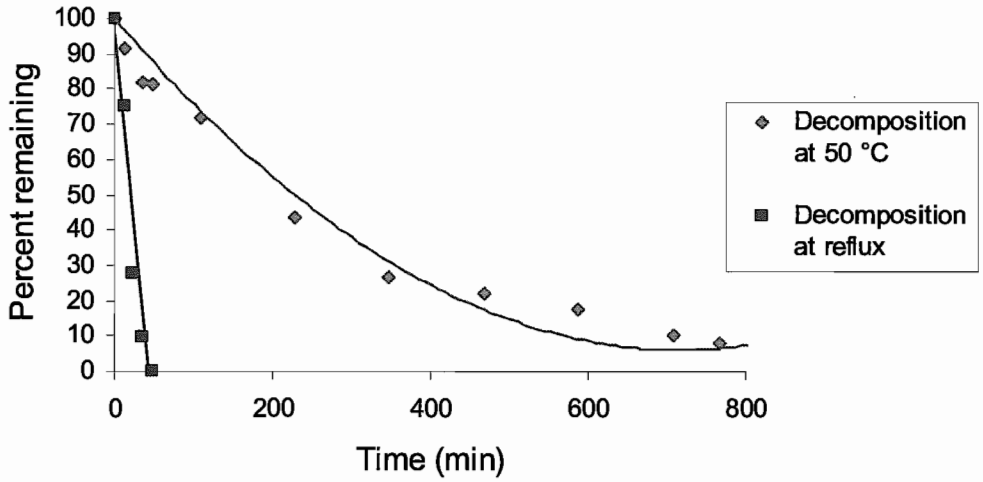



**Figure 82-** Decomposition of **1** at 50 °C and at reflux

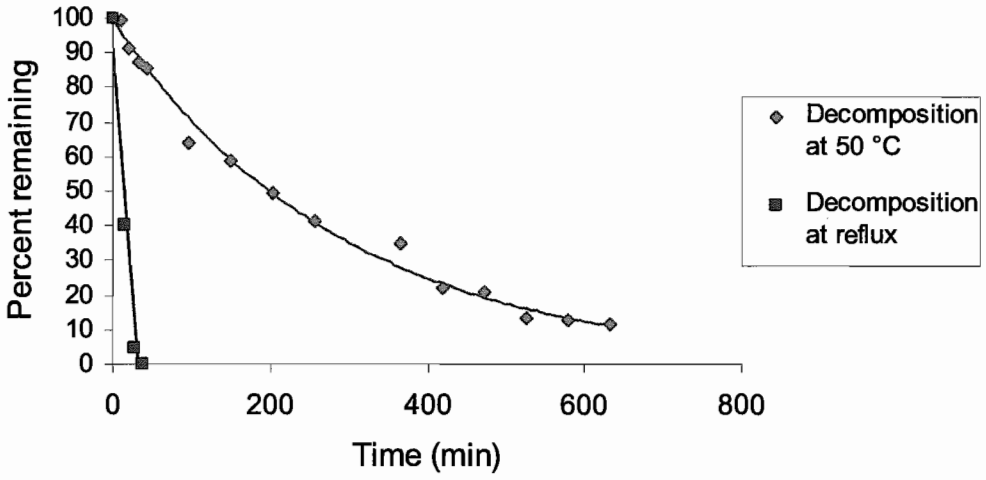



**Figure 83-** Decomposition of **124** at 50 °C and at reflux

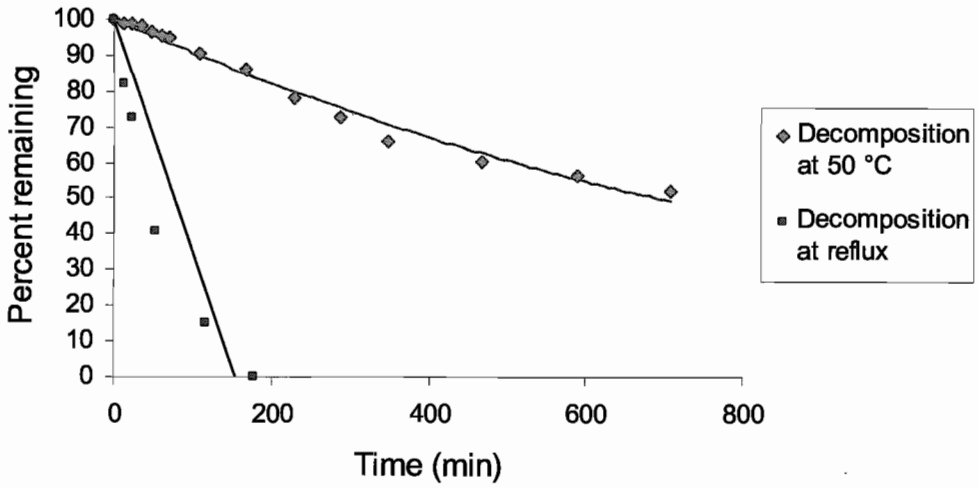



**Figure 84**- Decomposition of **312** at 50 °C and at reflux

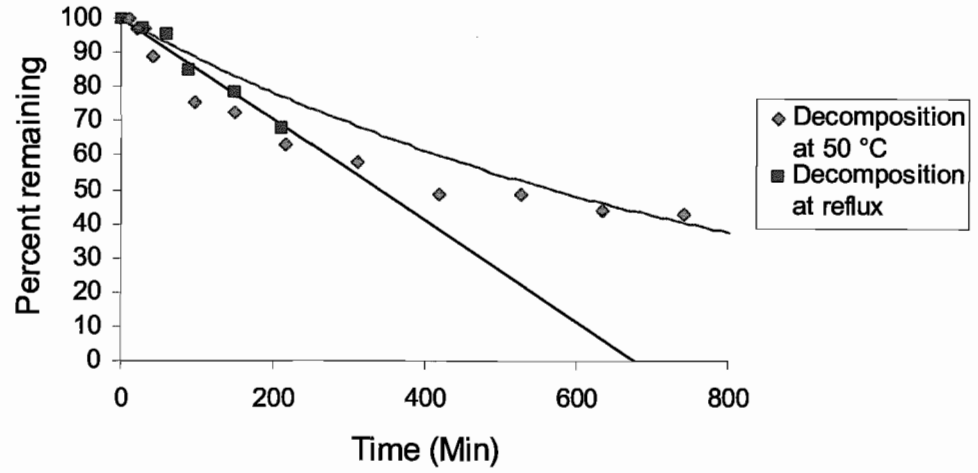



**Figure 85**- Decomposition of **313** at 50 °C and at reflux

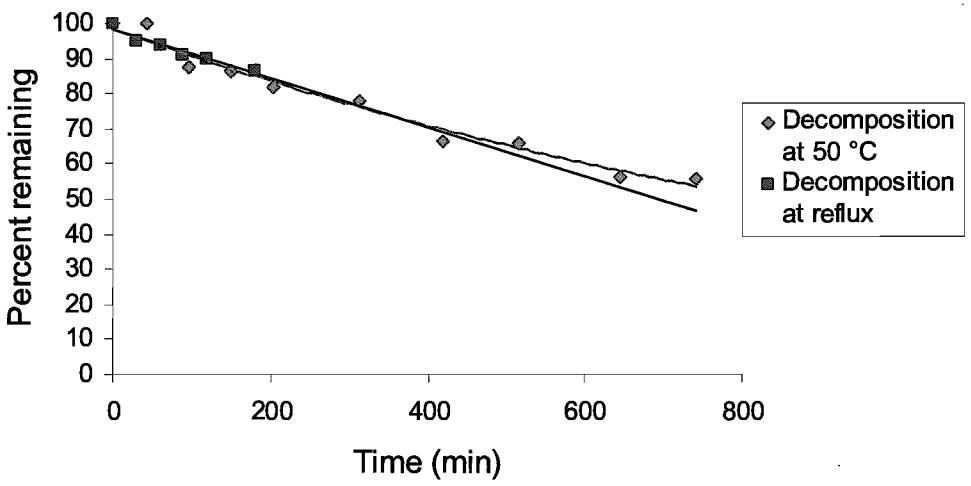



**Figure 86**- Decomposition of **314** at 50 °C and at reflux

The rapid decomposition of reagents **1** and **124** explain why yields of sulfamidates from epoxides are often low compared to the yields of sulfamidates from 1,2-diols. The decomposition studies as well as the reactivity profiles show that reagents **312** and **313** are likely the most useful to synthetic chemists. The minor increase in stability of reagent **314** does not offer any advantages in reactivity at least in the cases involving oxiranes.

### 3.4 Synthesis of morphine C-ring fragment

The synthesis of the C-ring of morphine (**3**), as outlined in the Introduction on page 2, began with the microbial oxidation of bromobenzene (**13**) to diol **12**. Fermentation took place in a 15 L Biostat fermentor (12 L working volume). Approximately 20 g/L diol was isolated from the fermentation. Diol **12** was then subjected to diimide reduction of the distal double bond to give diol **328**. The distal hydroxyl group was then protected as a silyl ether **329**. The proximal hydroxyl group was then coupled to Boc-protected glycine. A Kazmaier-Claisen rearrangement was then performed to give amino acid **330**. The crude amino acid was then methylated with diazomethane to give the C-ring fragment as a mixture of diastereomers **10** (Figure 82).

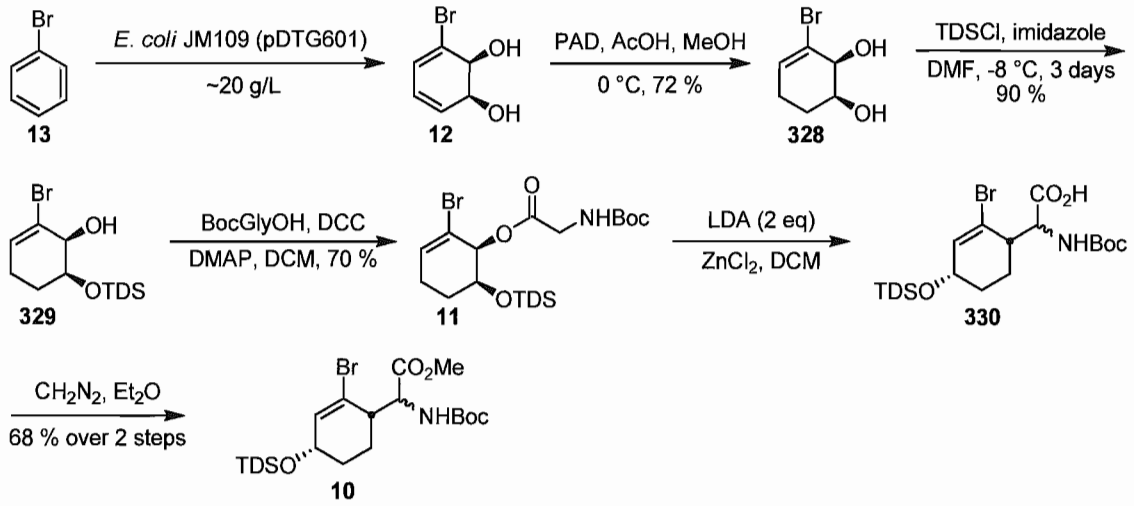



**Figure 87**-Synthesis of the C-ring fragment of morphine

Diastereomeric mixture **10** was separated by column chromatography to give C-ring fragment **9** and its diastereomer **331** in a 1:4 ratio. The undesired diastereomer **331** was then recycled by epimerization and separation (Figure 83).

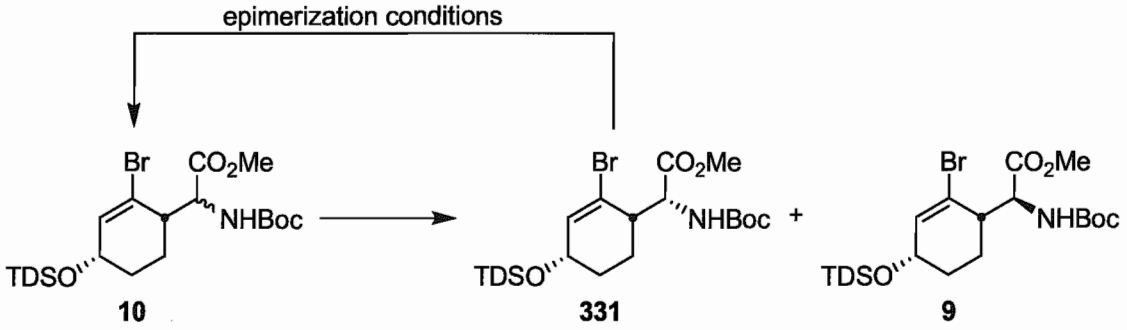



**Figure 88**-Separation of diastereomers and recycling of **331**

The original epimerization conditions took five days to complete and gave a 2:1 ratio of **331**:**9**. This became a significant bottleneck in the synthesis of **9**, so we undertook an optimization of the epimerization (Table 2). In Table 2, the yield refers to the total recovery of both diastereomers. Changing the solvent from THF to DME (entries 2-4) allowed the time to be decreased from five to three days. Increasing the equivalents of DBU helped to improve the ratio of **331**:**9** but led to slightly lower recovery (entries 3-4). A neat reaction in DBU led to major decomposition (entry 5). This data led us to determine that the optimal conditions, were 0.5 eq DBU in DME for three days (entry 4). These conditions gave us a good *dr*, shorter reaction times than the original conditions, and low decomposition.

**Table 2**-Optimization of epimerization conditions of **331**

| Entry | Solvent | eq DBU | Temperature (°C) | Time (d) | Yield of **10** (%) | Ratio **331:9** |
|---|---|---|---|---|---|---|
| 1 | THF | 0.1 | 66 | 5 | 80 | 2:1 |
| 2 | DME | 0.1 | 85 | 3 | 85 | 2:1 |
| 3 | DME | 1 | 85 | 3 | 70 | 1:1 |
| **4** | **DME** | **0.5** | **85** | **3** | **80** | **1:1** |
| 5 | neat | excess | 120 | 2 | 20 | 1:1 |

### 3.5 Coupling of A-ring fragment

With the C-ring fragment **9** in hand, we went on to explore the preparation of the A-ring fragment **8** and the coupling of **8** and **9**. Our original preparation of **8** involved a

three step sequence starting from guaiacol (**332**). This sequence however gave **8** in only 30 % yield and unreacted guaiacol was difficult to remove. A search of the literature yielded a one step preparation of **8** by Snieckus[155]. Snieckus' procedure involves a directed *ortho* metalation of 1,2-dimethoxybenzene (**335**) followed by quenching with trimethylborate (Figure 84). This one-pot procedure gave **8** in 85 % yield and was easily performed on a multi-gram scale.

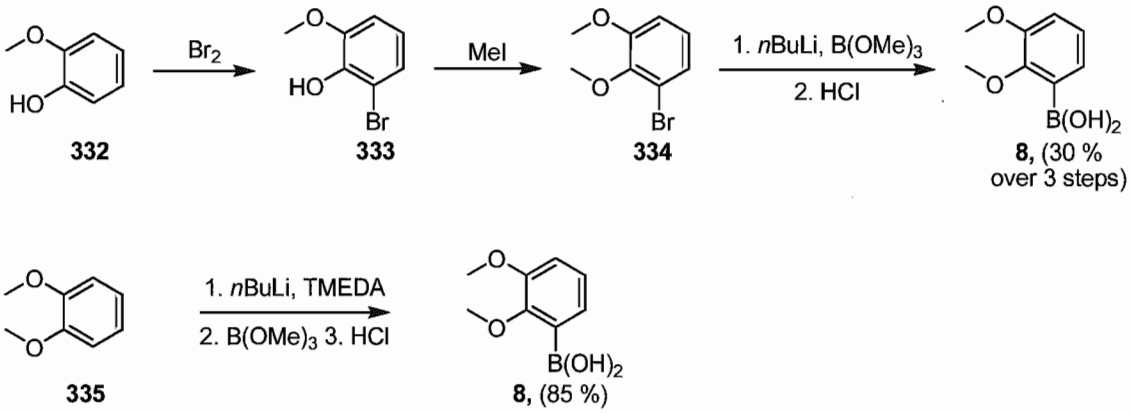



**Figure 89**-Preparation of A-ring fragment **8**

The A-ring (**8**) and C-ring (**9**) fragments were then joined by a Suzuki coupling (Figure 85). The initial conditions employed a biphasic reaction in benzene and water. However, the yields were not always reproducible and we worried about hydrolysis of the methyl ester. The conditions were optimized as shown in Table 3. The palladium tetrakis(triphenylphosphine) varied between batches and seemed to have an effect on yields and was therefore replaced with $Pd(dppf)_2$. The use of $Pd(dppf)_2Cl_2$ and CsOAc in THF gave reproducible reactions in good yield. Substituting CsOAc for $Cs_2CO_3$ improved the yield by a further 19 %.

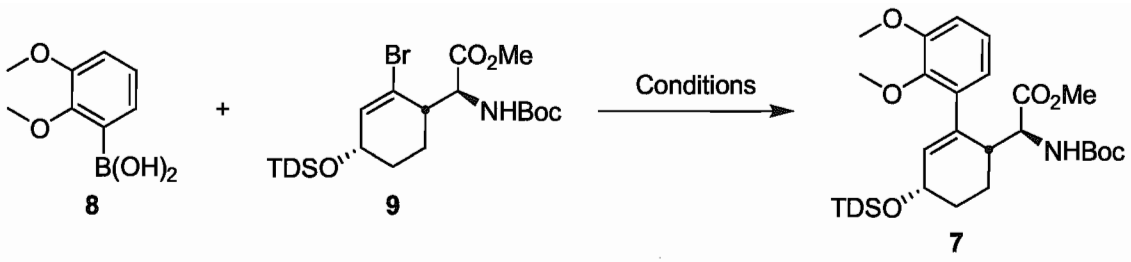



**Figure 90**-Suzuki coupling of **8** and **9**

**Table 3**-Optimization of Suzuki coupling

| Entry | Solvent | Catalyst | Base | Phase transfer agent | Yield (%) |
|---|---|---|---|---|---|
| 1 | benzene | $Pd(PPh_3)_4$ | $Na_2CO_3$ (aq) | TBAB | 60-75 |
| 2 | THF | $Pd(dppf)_2Cl_2$ | CsOAc | none | 70 |
| 3 | THF | $Pd(dppf)_2Cl_2$ | $Cs_2CO_3$ | none | 89 |

### 3.6 Synthesis of Claisen substrates

Several substrates for the Johnson-Claisen rearrangement were synthesized from intermediate **7**. The first substrate synthesized was alcohol **338**. This was done by removing the silyl ether of **7** followed by a Mitsunobu reaction to invert the stereochemistry of the alcohol. Deprotection proceeded smoothly and the product of the Mitsunobu reaction **337** was obtained in good yield. Hydrolysis of the benzoate ester in methanol gave **338** in 85 % yield (Figure 86).

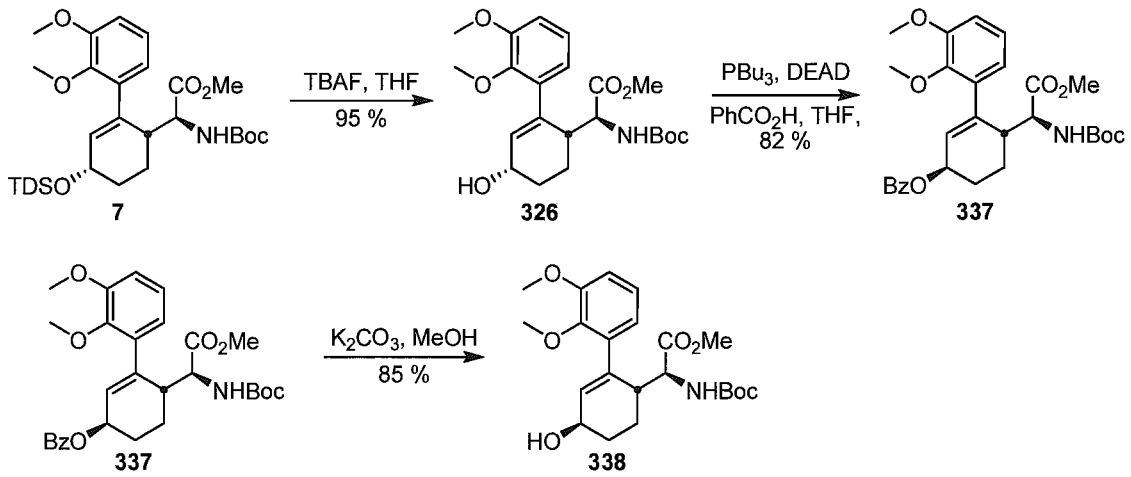



**Figure 91**-Synthesis of alcohol **338**

The next substrate synthesized for the Claisen rearrangement was acetate **340**. This was prepared by simultaneously removing the benzyl ester and Boc protecting groups of **337** to give free amine **339** and then re-protecting the amine as its acetate (Figure 87).

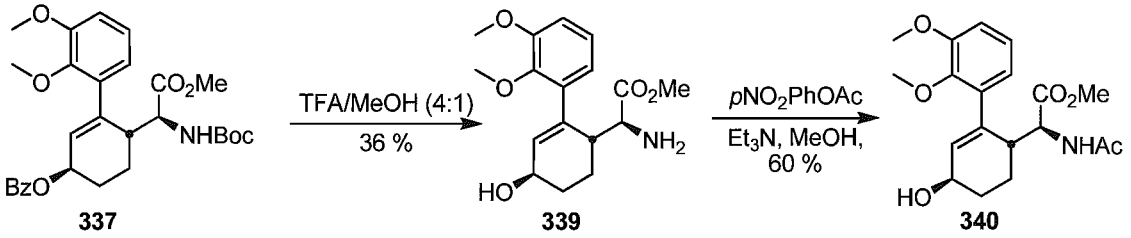



**Figure 92**-Preparation of Claisen substrate **340**

The final Claisen substrate prepared was cyclic carbamate **6**. Diester **337** was reduced with lithium aluminum hydride to give alcohol **341**. Treatment of **341** with two equivalents of sodium hydride gave carbamate **6** in 80 % yield (Figure 88).

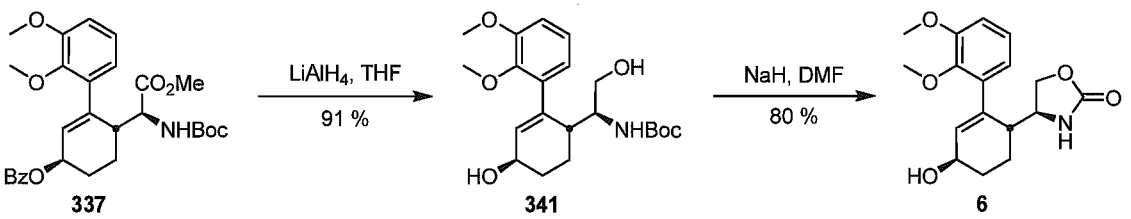
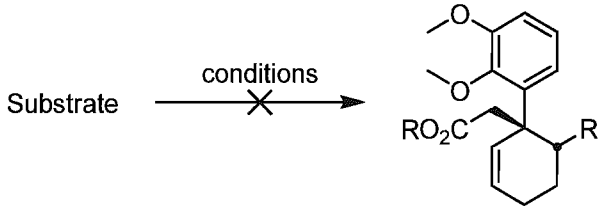



**Figure 93**-Preparation of cyclic carbamate **6**

### 3.7 Claisen rearrangement

All attempts at performing the planned Johnston-Claisen rearrangement failed to yield the desired rearranged product of type **342** (Figure 89). The results of several attempts are shown in Table 4.

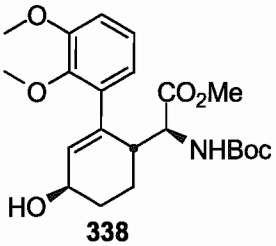
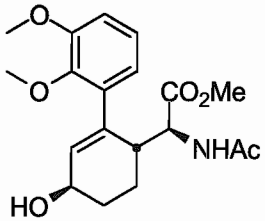
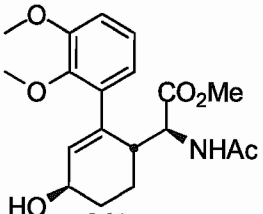
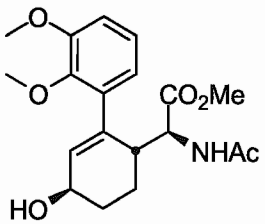
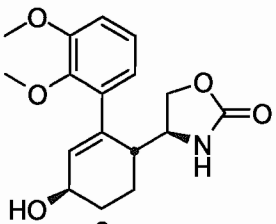
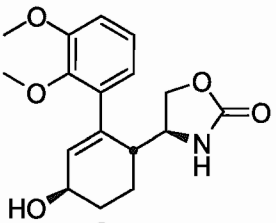
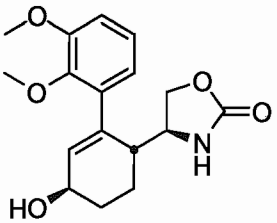
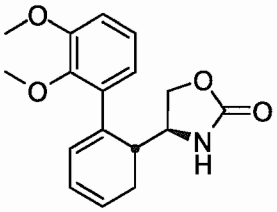



**342**

**Figure 94**-Attempted Johnson-Claisen rearrangement

The first substrate tested in the Claisen rearrangement was **338**. The substrate was subjected to the conditions employed in Chida's synthesis of morphine.[74] Unfortunately the high temperature and acidic conditions led to the loss of the Boc protecting group. The only product isolated was acetamide **340** in a very low yield. We then attempted the rearrangement on **340** but after three days only starting material was isolated. We then turned our attention to cyclic carbamate **6**. Our rationale was that the C-13 (morphine numbering) position would be more accessible without the steric bulk of the methyl ester and amine. Unfortunately, repeating Chida's conditions on **6** led only to decomposition. We then subjected **6** to more traditional Johnson-Claisen conditions, using propionic acid and triethyl orthoacetate. These conditions also lead to decomposition. In the final attempt at the rearrangement, we used McGreary and Cosgrove's TIBAL catalyzed Johnson-Claisen rearrangement.[145] This reaction led only to the elimination of the hydroxyl group to a diene (Table 4). At this point, it is believed that the nitrogen atom must have some effect that prevents the rearrangement as the presence of nitrogen is the only major difference between our Claisen substrates and Chida's.

**Table 4**-Substrates and conditions attempted in Johnson-Claisen rearrangement

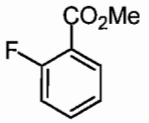
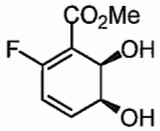
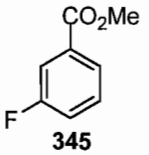
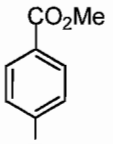
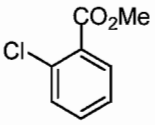
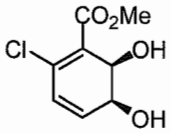
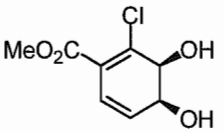
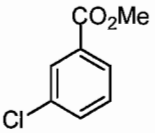
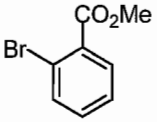
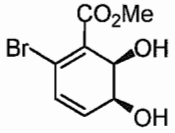
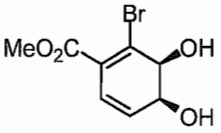
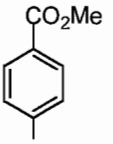
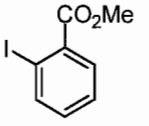
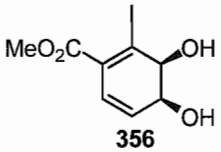
| Substrate | Conditions | Product |
|---|---|---|
|  **338** | trimethyl orthoacetate, *o*-Nitrophenol (10 mol %), 140 °C, 3 days |  **340**, ~5 % |
|  **340** | trimethyl orthoacetate, *o*-Nitrophenol (10 mol %), 140 °C, 3 days |  **340**, 60 % |
|  **6** | triethyl orthoacetate, *o*-Nitrophenol (10 mol %), 140 °C, 3 days | decomposition |
|  **6** | triethyl orthoacetate, propionic acid (10 mol %), 160 °C, 3 days | decomposition |
|  **6** | 1. Diethyl ketene acetal, neat, rt, 2 hours<br>2. TIBAL (1 eq), rt, 14 hours |  40 % |

### 3.8 Biotransformations

A series of halogen substituted benzoate esters were tested as substrates of TDO. The substrates were first tested in Fernbach shake flasks. Approximately 100 mg was incubated with *E. coli* JM109(pDTG601) at 35 °C for 6 hours. The appearance of metabolites was followed by TLC. In the event that the ester was metabolized, cells were separated from the broth by centrifugation and the supernatant was extracted with EtOAc and a preliminary NMR spectrum was acquired. A large scale fermentation was then performed with the particular substrate and the metabolites were characterized. As shown in Table 5, all *meta-* and *para*-substituted benzoates were not metabolized. *Ortho*-substituted benzoates were found to be substrates although the metabolites were produced in relative low yields compared to the 1.3 g/L yield of unsubstituted methyl benzoate.[94] Fluoro-substituted benzoate **343** yielded only one metabolite while chloro- and bromo-substituted benzoates **347** and **351** gave a mixture of diols. Iodo- substituted methyl benzoate **355** gave only a single metabolite. This trend is in accordance with Boyd's model for predicting the regio-chemistry of dihydroxylation by TDO.[89] In the case of **343**, the ester directs the regiochemistry of dihydroxylation. The increasing steric bulk of chlorine and bromine lead to a mixture of metabolites and in the case of iodine substituted benzoate **355** the iodine atom directs dihydroxylation. At the time of this writing, the absolute stereochemistry of the isolated metabolites has not yet been determined. The relative stereochemistry of all metabolites was determined by 2D NMR (H,H COSY, HSQC, and HMBC). The physical and spectral properties of **344** have been fully characterized and preliminary characterization has been achieved for metabolites **348**, **349**, **352**, **353**, and **356**. It was found that like the diols isolated from the

fermentation of unsubstituted benzoate esters (**249**), metabolites where dihydroxylation occurred adjacent to the ester (**344**, **348**, and **352**) were stable at room temperature and amenable to purification by column chromatography. Metabolites that possessed dihydroxylation adjacent to the halogen atom (**349**, **353**, and **355**) were much less stable and upon chromatography, would re-aromatize to give phenols.

**Table 5**-Metabolism of halogen substituted benzoate esters by TDO

| Starting material | Products (Yield) |
|---|---|
|  **343** |  **344** (0.05 g/L) |
|  **345** | No conversion |
|  **346** | No conversion |
|  **347** |  **348** (0.47 g/L)  **349** (.035 g/L) |
|  **350** | No conversion |
|  **351** |  **352**  **353** |
|  **354** | No conversion |
|  **355** |  **356** |

## 4. Conclusions and future work

We have developed the synthesis for and measured the stability of several Burgess reagents and tested their reactivity towards epoxides, diols and in dehydration reactions. We found that reagents **312** and **313** are likely to be the most useful to synthetic chemists in terms of stability and reactivity towards alcohols, epoxides, and diols. Other variants of the Burgess reagents such as Nicolaou's reagents **98a-e** and Wipf's PEG supported reagent **118** may benefit from increase in stability by replacing the triethylamine portion of the reagent with *N*-methylpiperidine.

Our proposed synthesis of morphine (**3**) proceeded to the Johnson-Claisen rearrangement step which was ultimately unsuccessful. As shown in Figure 90, the Johnson-Claisen substrates described in this thesis differ only slightly from Chida's intermediate **219**. The presence of a carbamate may prevent the reaction from proceeding as envisioned. The carbamate may also impart lower stability on our substrates thus leading to the decomposition observed in several of our reactions.

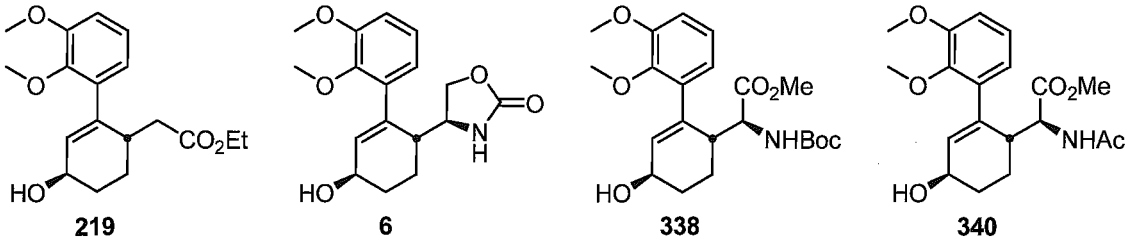



**Figure 95**-Chida's intermediate compared to Claisen substrates prepared in this thesis

Another strategy would be the preparation of a diene of type **357** followed by a cycloadditions of a ketene acetal. Methylation of the nitrogen atom to produce **360** may prevent the problems encountered in performing the Johnson-Claisen rearrangement (Figure 91). Work on the completion of the synthesis is currently being undertaken by Mr. Vimal Varghese.

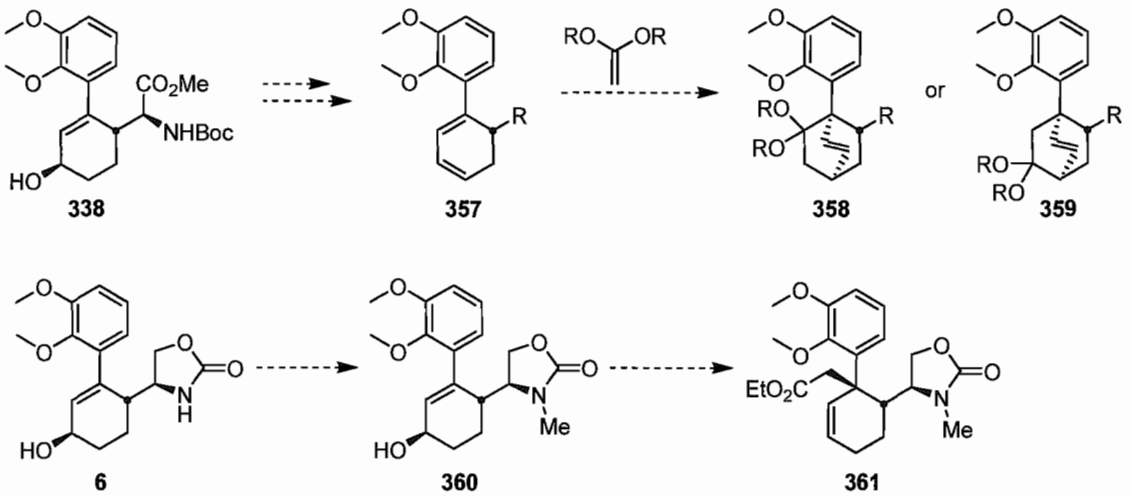



**Figure 96**-Proposed cycloaddition strategy and methylated Claisen substrate for the completion of the synthesis of morphine

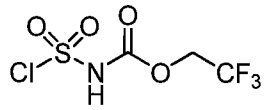
Several new metabolites of toluene dioxygenase have been discovered. More complete characterization, proof of absolute stereochemistry and optimization of the fermentation procedure need to be undertaken by future workers in this area.

## 5 Experimental section

### 5.1 General

All non-hydrolytic reactions were carried out under an inert atmosphere. Glassware used for moisture-sensitive reactions was flame-dried under vacuum and subsequently purged with inert gas. THF, toluene and benzene were distilled from sodium/benzophenone. DCM, triethylamine, and *N*-methylpiperidine were distilled over calcium hydride. Flash column chromatography was performed using Silicycle Siliaflash P60 230-400 mesh silica gel. Analytical thin-layer chromatography was performed using EMD Chemicals TLC Silica Gel 60 $F_{254}$ plates. Melting points were measured on a Thomas-Hoover melting point apparatus and are reported uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR 1600 Series Spectrum One instrument. $^{1}H$ and $^{13}C$ NMR spectra were obtained on either a 300 MHz Bruker or a 600 MHz Bruker instrument. Mass spectra were acquired on a Kratos Concept 1S High Resolution E/B mass spectrometer. Ionization methods were either electron impact (EI) or fast atom bombardment (FAB) on a *N*-bromo-acetamide (NBA) matrix. Specific rotation measurements are given in deg. $cm^3$ $g^{-1}$ $dm^{-1}$ and were recorded on a Perkin-Elmer 341 Polarimeter. Large scale fermentation was performed in a 15 L Sartorius (formerly B. Braun) Biostat C fermentor. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA, U.S.A.

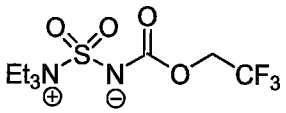
## 5.2 Preparation of new Burgess reagents



316

### 2,2,2-Trifluoroethyl chlorosulfonylcarbamate (316)

2,2,2-Trifluoroethanol (3.36 mL, 46 mmol) in dry benzene (10 mL) was added dropwise to chlorosulfonyl isocyanate (4.0 mL, 46 mmol) in 15 mL of dry benzene at room temperature. When the addition was complete, the reaction mixture was stirred for 30 min. The product, 2,2,2-trifluoroethyl chlorosulfonylcarbamate (**316**), was precipitated with cold hexanes as white crystals (10.25 g, 42 mmol, 92%); mp 80-82 °C ($C_6H_6$); $^1$H NMR($CDCl_3$, 300 MHz) δ 8.44 (m, 1H), 4.66 (q, *J*= 7.9 Hz, 2H) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 147.7, 122.0 (q, *J*= 278.8 Hz), 62.9 (q, *J*= 38.6 Hz) ppm; IR (KBr) *v* 3167.6, 2931.6, 2637.9, 1750.3, 1483.9, 1396.8, 1166.0 cm$^{-1}$; LRMS (FAB+NBA matrix) m/z 242, 149 (18.9), 99 (41.3), 73 (25.9), 59 (80.8), 49 (100.0); HRMS calcd. for $C_3H_4ClNF_3O_4$: 241.9423, found: 241.9496

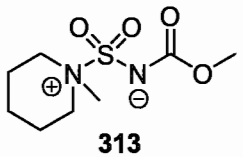


312

### *N*,*N*-Diethyl-*N*-[(2,2,2-trifluoroethyloxycarbonyl)amino]sulfonyl-ethanaminium, inner salt (312)

2,2,2-Trifluoroethyl chlorosulfonylcarbamate (**316**) (2.0 g, 8.3 mmol) in 50 mL dry THF was added dropwise to triethylamine (2.90 mL, 20.8 mmol) in 20 mL dry THF in an ice bath. Once the addition was complete, the reaction was stirred for additional two hours. Triethylammonium chloride salt was filtered and the solvent removed *in vacuo*. The

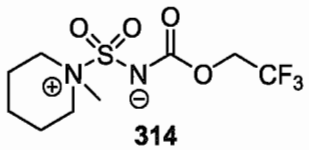
product (**312**) was recrystallized twice from dry THF (1.91 g, 6.2 mmol, 75 %); mp 77-79 °C (THF); $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.48 (d, *J*= 8.6 Hz, 2H) 3.84 (q, *J*= 7.8 Hz, 6H) 1.44 (t, *J*= 9.5 Hz, 9H) ppm; $^{13}$C NMR (THF($d_8$) , 150 MHz) δ 155.4, 123.8 (q, *J*= 277.4 Hz), 60.1 (q, *J*= 35.8 Hz), 50.6, 8.5 ppm; IR (KBr) *v* 3167.6, 2986.1, 2931.6, 2676.8, 2637.9, 2107.9, 1750.3, 1691.2 cm$^{-1}$; LRMS (FAB+NBA matrix) *m/z* 307, 239 (30.8), 102 (100.0), 86 (20.0); HRMS calcd. for $C_9H_{18}F_3N_2O_4S$: 307.0934, found: 307.0930.



**313**

**N-Methyl-N-[(methyloxycarbonyl)amino]sulfonyl piperidinaminium, inner salt (313)**

Methyl chlorosulfonylcarbamate (**315**) (6.83 g, 39 mmol) in benzene (30 mL ) was added dropwise to *N*-methylpiperidine in benzene (20 mL) cooled in an ice bath. Once the addition was complete, the reaction was stirred for additional two hours. *N*-Methyl piperidinium chloride salt was filtered off and the solvent was removed *in vacuo*. The product was recrystallized two times from dry THF to yield **313** (6.6 g, 28 mmol, 71 %); mp 87-90 °C (THF); $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 3.60 (m, 2H), 3.45 (m, 2H) 3.14 (s, 3H) 1.81-2.00 (m, 6H) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 158.2, 54.7, 53.3, 40.1, 21.6, 20.6 ppm; IR (KBr) *v* 3206.4, 2951.4, 2869.3, 2686.4, 2110.2, 1704.5, 1470.7 cm$^{-1}$; LRMS (FAB+NBA matrix) *m/z* 237, 205 (34.3), 100 (100.0), 70 (11.2).



**314**

***N*-Methyl-*N*-[(2,2,2-trifluoroethyloxycarbonyl)amino]sulfonyl-piperidinaminium, inner salt (314)**

2,2,2-Trifluoroethyl chlorosulfonylcarbamate (**316**) (4.0 g, 17 mmol) in 30 mL dry THF was added dropwise to *N*-methylpiperidine (3.80 g, 38 mmol) in 20 mL dry THF at 0 °C. Once the addition was complete, the reaction was stirred for an additional two hours. *N*-Methylpiperidinium chloride salt was filtered off and the solvent removed *in vacuo*. The product was recrystallized two times from dry THF to yield **314** (2.4 g, 7.9 mmol, 48 %); mp 79-81°C (THF); $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 4.48 (q, *J*= 8.5 Hz, 2H), 3.63 (m, 2H), 3.45 (m, 2H), 3.15 (s, 3H), 1.82-1.99 (m, 6H) ppm; $^{13}$C NMR ($CDCl_3$ , 150 MHz) δ 156.1, 123.2 (q, *J*= 277.8 Hz), 61.7 (q, *J*= 36.0 Hz), 54.8, 40.2, 21.4, 20.6 ppm; IR (KBr) *v* 3425.3, 2964.1, 2872.7, 2716.4, 2127.0, 1712.9, 1470.3 $cm^{-1}$; LRMS (FAB+ NBA matrix) *m/z* 305, 205 (26.7), 137 (3.9), 100 (100.00); HRMS calcd. for $C_9H_{15}F_3N_2O_4S$: 305.0783, found: 305.0764.

**General procedure for dehydration of 1,2,3,4 tetrahydro-1-naphthol with Burgess reagents**

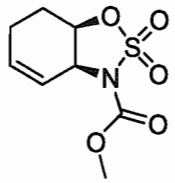
1,2,3,4-Tetrahydro-1-naphthol (1.83 mmol) and Burgess reagent (2.10 mmol) were dissolved in dry benzene (5 mL) at room temperature, the reaction mixture was brought to reflux temperature and monitored by TLC. Reactions were stopped after 2 hours.

**General procedure for reactions of Burgess reagents with oxiranes**

The appropriate Burgess reagent inner salt (9.2 mmol) was added to a stirred solution of the oxirane (4.0 mmol) in THF (20 mL) at room temperature in a single portion. The resulting reaction mixture was brought to reflux immediately by submerging it into a preheated oil bath (80 °C). The reaction mixture was stirred until complete consumption of the oxirane (TLC), then cooled to room temperature and filtered through a plug of silica. The reaction mixture was concentrated, and the resulting residue was purified by flash column chromatography using an appropriate solvent gradient to yield the sulfamidate product(s).

**General procedure for reactions of Burgess reagents with diols**

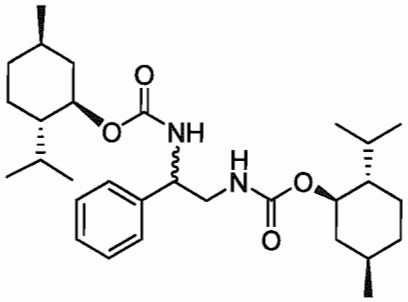
1-Phenyl-1,2-ethanediol (3.7 mmol, 1.0 equiv) was dissolved in anhydrous THF (10 mL) and Burgess reagent (9.3 mmol, 2.5 equiv) was added. The resulting solution was warmed to reflux (using an oil bath preheated to 80 °C) and stirred for 2 to 8 hours until the diol was completely consumed (TLC). The reaction was quenched with a saturated solution of $NH_4Cl$ (5 mL) and the mixture was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were then washed with water (50 mL), dried over $Na_2SO_4$ and concentrated. The resultant yellow oil was purified by flash column chromatography (silica gel) using an appropriate solvent system.



319

**Methyl *cis*-tetrahydro-3*H*-1,2,3-benzoxathiazole-3-carboxylate 2,2-dioxide (319)**

Eluent: hexanes-ethyl acetate, 4:1; $R_f$ 0.42 (2:1 Hex:EtOAc); mp 145-147 °C (EtOAc); $^1$H NMR ($CDCl_3$, 600 MHz) δ 6.12 (m, 1H), 5.81 (d, $J$= 10.32 Hz, 1H), 5.21 (s, 1H), 4.80 (s, 1H), 3.93 (s, 3H), 2.35 (m, 1H), 2.30 (m, 1H), 2.15 (m, 1H), 1.92 (m, 1H) ppm; $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 150.5, 131.6, 120.7, 77.8, 55.5, 54.6, 24.0, 18.5 ppm; IR (KBr) $v$ 3438.9, 3010.2, 2963.5, 2853.3, 2544.9, 1725.9 cm$^{-1}$; LRMS (FAB+NBA matrix) *m/z* 234, 214 (13.5), 156 (27.4), 79 (40.3); HRMS calcd. for $C_8H_{12}NO_4S$ 234.0436, found: 234.0394. Anal. calcd for $C_8H_{11}NO_5S$: C 41.20, H 4.75. Found: C 41.32, H 4.75.

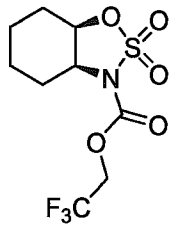


322

**Bis-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 1-phenylethane-1,2-diyldicarbamate (322)**

$R_f$ 0.75 (1:1 Hex:EtOAc); mp 173-175 °C (EtOAc); $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 2H), 7.29 (m, 3H), 5.72 (m, 1H), 4.82 (m, 2H), 4.56 (m, 2H), 3.52 (s, 2H), 2.01 (m, 4H), 1.69 (m, 5H), 1.51 (s, 3H), 1.32 (m, 2H) 0.95 (m, 24H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 128.7, 127.7, 126.3, 75.0, 74.8, 56.4, 47.3, 41.4, 34.3, 31.4, 26.3, 23.5, 22.0,

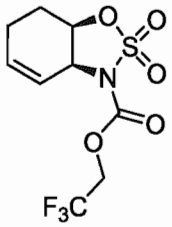
20.9, 16.4; IR (KBr) $\nu$ 1015.2, 1148.8, 1291.1, 1455.0, 1533.1, 1685.8, 2956.1, 3364.2 $cm^{-1}$; LRMS (FAB+NBA matrix) *m/z*, 501(11.3), 319 (22.1), 225 (24.3), 181 (69.9), 120 (38.0), 83 (100.0); Anal. calcd for $C_{30}H_{48}N_2O_4$: C 71.96, H 9.66, N 5.59, found: C 71.70, H 9.78, N 5.60.



**323**

**2,2,2, Trifluoroethyl *cis*-hexahydro-3*H*-1,2,3-benzoxathiazole-3-carboxylate 2,2-dioxide (323)**

Eluent: hexanes-ethyl acetate, 2:1; $R_f$ 0.45 (2:1 Hex:EtOAc); mp 83-85 °C (EtOAc); $^1H$ NMR ($CDCl_3$, 600 MHz) δ 5.07 (d, *J*= 3.1 Hz, 1H), 4.69 (m, 1H), 4.61 (m, 1H), 4.27 (m, 1H), 2.38 (m, 1H), 2.33 (m, 1H), 1.90 (m, 1H), 1.81 (m, 2H), 1.69 (m, 1H), 1.55 (m, 1H), 1.27 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 148.3, 122.3 (q, *J*= 278.8 Hz), 80.0, 62.5 (q, J = 37.6 Hz), 58.4, 26.9, 21.8, 18.8; IR (KBr) $\nu$ 3031.7, 2947.2, 2871.5, 1755.5, 1623.1 $cm^{-1}$; LRMS (FAB+NBA matrix) *m/z* 304, 258 (5.5), 224 (43.3), 136 (30.7), 81 (100.0); HRMS calcd. for $C_9H_{13}F_3NO_5S$: 304.0512, found: 304.0467; Anal. calcd for $C_9H_{12}F_3NO_5S$: C 35.65, H 3.99, found: C 35.74, H 3.98.



**324**

**2,2,2-Trifluoroethyl *cis*-tetrahydro-3*H*-1,2,3-benzoxathiazole-3-carboxylate 2,2-dioxide (324)**

Eluent: hexanes-ethyl acetate, 2:1; $R_f$ 0.46 (2:1 Hex:EtOAc); mp 70-72 °C (EtOAc); $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.15 (m, 1H), 5.79 (d, *J*= 10.2 Hz, 1H), 5.24 (s, 1H), 4.85 (s, 1H), 4.65 (m, 2H), 2.29 (m, 2H), 2.09 (m, 1H), 1.85 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 148.6, 132.3, 122.3 (q, *J*= 277.7 Hz), 120.1, 78.1, 62.5 (q, *J*= 37.6 Hz), 55.7, 27.1, 23.9, 18.5; IR (KBr) *v* 3492.1, 3044.8, 2982.3, 2933.8, 2853.8, 1766.9 cm$^{-1}$; LRMS (EI) *m/z* 301, 221 (33.5), 220 (18.4), 216 (14.2), 120 (21.5), 94 (30.0), 78 (100.0); HRMS calcd. for $C_9H_{10}F_3NO_5S$: 301.0232, found: 301.0229; Anal. calcd for $C_9H_{10}F_3NO_5S$: C 35.88, H 3.35, found: C 35.98, H 3.24.

## 5.3 Stability studies

### NMR data collection protocol

The $^{13}C$ NMR spectra were acquired on a Bruker Avance AV600 spectrometer equipped with a BBO-Z grad probe and VT accessory. A series of $^{13}C$ NMR spectra were recorded for each reagent using a power gated proton decoupling pulse sequence from the Bruker library with a 30 degree flip angle and a 2 s relaxation delay. Each spectrum was acquired using 256 transients, 16K data points with a spectral width of 238 ppm, a line broadening of 1Hz and zero filled to 32K points. The acquisition time for each spectrum was 11 minutes. All spectra were processed and analyzed using Bruker Topspin2.1 PL4 software running on a Windows XP workstation.

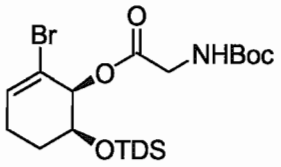
### Decomposition study of Burgess reagents at 50 °C

100 mg of Burgess reagent was dissolved in 0.75 mL $d^8$- THF in an NMR tube. $^{13}C$ proton decoupled spectra were acquired at 12 minute intervals on the 600 MHz spectrometer. The integral of the carbonyl peak was compared to that of the solvent peak at 64.6 ppm to determine the percentage of reagent remaining in each spectrum.

### Decomposition study of Burgess reagents at 78 °C

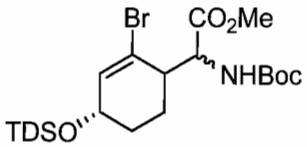
Six identical reactions were set up in microreactor vials. 100 mg of Burgess reagent was dissolved in 0.75 mL $d^8$- THF. The reaction vials were placed in a pre-heated microreactor block. At 12 minute intervals, one vial was removed, cooled in liquid nitrogen and transferred to a dried NMR tube and a $^{13}C$ proton decoupled NMR spectrum was acquired. The percentage of intact Burgess reagent remaining was determined by comparing the integral of the carbonyl peak to that of the solvent peak at 64.6 ppm.

**5.4 Intermediates in morphine synthesis**



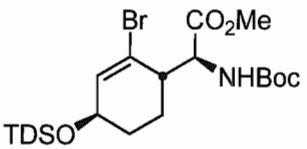

**11**

A solution of Boc-glycine (12.0 g, 70 mmol), DCC (18.5 g, 90 mmol) and DMAP (85 mg, 7 mmol) in DCM (200 mL) was cooled to 0 °C and a solution of TDS protected diol **329** (15.0 g, 45 mmol) in DCM (200 mL) was added slowly over a period of 10 min. The reaction mixture was stirred for 14 hours warming to rt. The solution was diluted with $Et_2O$ (200 mL) and filtered through a plug of silica to remove dicyclohexyl urea. The solvent was removed under reduced pressure and chromatographed on silica gel with hexanes:ethyl acetate 9:1 as the eluent. The product **11** was isolated as a colorless oil (15.4 g, 31.5 mmol, 70 %). $R_f$ 0.7 (4:1 Hex:EtOAc); $[\alpha]_D^{20}$ -64.0 (c = 1.0, MeOH); $^1$H NMR $CDCl_3$, 300 MHz) δ 6.27 (dd, $J$ = 5.2, 3.1 Hz, 1H), 5.59 (d, $J$ = 3.9 Hz, 1H), 5.00 (bs, 1H), 3.97 (m, 3H), 2.39-2.19 (m, 1H), 2.15-2.09 (m, 1H), 1.85-1.62 (m, 2H), 1.43 (s, 9H), 0.84 (s, 3H), 0.82 (s, 3H), 0.77 (d, $J$ = 1.9 Hz, 6H), 0.07 (d, $J$ = 4.6 Hz, 6H) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 169.6, 155.3, 134.8, 117.0, 79.6, 73.9, 69.2, 42.3, 34.0, 28.2, 25.5, 24.7, 22.6, 20.0, 18.5, -3.1, -3.15 ppm; IR (film) $v$ 3445, 2958, 1755, 1715, 1511 cm$^{-1}$; LRMS (EI) *m/z* 171 (7), 157 (9), 136 (34), 121 (9), 79 (10), 28 (100); HRMS calcd. for $C_{21}H_{39}NSiBrO_5$(M+H): 492.1781, found: 492.1806; Anal. calcd. for $C_{21}H_{38}NSiBrO_5$: C 51.21, H 7.78, found: C 51.41, H 7.75.




**10**

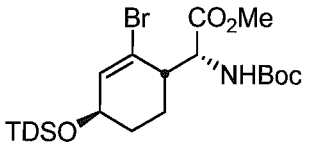
Glycine ester **11** (6g, 11.8 mmol) was dissolved in THF (100 mL). A solution of $ZnCl_2$ in THF (1.0 M, 19 mL, 19.0 mmol) was added and the mixture was cooled to -78 °C. A solution of LDA (2.2 M, 8.6 mL, 19.0 mmol) in THF was added dropwise. The reaction was stirred for 16 hours warming to room temperature. The reaction mixture was then acidified to a pH of approximately 2.5 with 1M HCl. The resulting solution was then extracted with $Et_2O$ (3 x 100 mL), washed with brine (20 mL), and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give amino acid **330** as a mixture of diastereomers. The unpurified acid was then treated with excess diazomethane. The resulting diastereomeric mixture of esters **10** was then chromatographed on silica gel with hexanes:ethyl acetate 20:1 to give enantiopure esters **9** and **321** in a ratio of 1:4 with a combined yield of 68 % over 2 steps.




**9**

Yield 3.25 g (1.6 mmol); $R_f$ 0.65 (4:1 Hex:EtOAc); $[\alpha]_D^{20}$ -27.7 (c = 1.0, $CHCL_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.27 (dd, $J$ = 5.6, 1.3 Hz, 1H), 4.81 (m, 2H), 4.12 (m, 1H), 4.11 (m, 1H), 3.71 (s, 3H), 2.96 (bs, 1H), 1.86-1.76 (m, 1H), 1.63-1.50 (m, 3H), 1.40 (s, 9H), 0.86 (d, $J$ = 6.9 Hz, 6H), 0.80 (s, 6H), 0.06 (d, $J$ = 5.3 Hz, 6H) ppm; $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 171.7, 155.4, 135.5, 127.9, 79.7, 65.4, 55.2, 52.2, 43.7, 34.1, 29.5, 28.2, 24.8, 20.2, 19.9, 18.5, -2.6, -3.0 ppm; IR (KBr) $\nu$ 3443, 2956, 2868, 1749, 1715 $cm^{-1}$; LRMS (EI) *m/z* 370 (13), 366 (38), 364 (37), 348 (16), 346 (15), 231 (24), 229 (24),

162 (95), 75 (100); HRMS calcd. for $C_{22}H_{41}NSiBrO_5$(M+H): 506.1920, found: 506.1937; Anal. calcd. for $C_{22}H_{40}NSiBrO_5$: C 52.16, 7.96, found: C 52.34, 8.01.

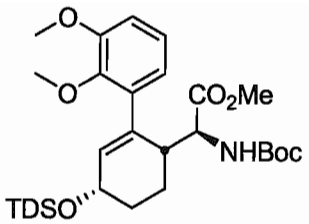



**331**

Yield 13.0 g (6.4 mmol); $R_f$ 0.7 (4:1 Hex:EtOAc); $[\alpha]_D^{20}$ -55.7 (c = 1.0, $CHCL_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.30 (dd, $J$ = 5.6, 1.3 Hz, 1H), 5.21 (d, $J$ = 8.6 Hz, 1H), 4.68 (dd, $J$ = 8.7, 2.3 Hz, 1H), 4.11 (m, 1H), 3.71 (s, 3H), 3.05 (bs, 1H), 1.86-1.78 (m, 2H), 1.63-1.50 (m, 2H), 1.43 (s, 9H), 0.84 (d, $J$ = 6.9 Hz, 6H), 0.80 (s, 6H), 0.05 (d, $J$ = 5.3 Hz, 6H) ppm; $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 171.9, 155.4, 136.3, 125.5, 80.0, 66.7, 55.9, 52.3, 45.1, 34.2, 29.2, 28.3, 25.8, 24.7, 23.4, 20.2, 18.6, -2.7, -2.9 ppm; IR (KBr) $\nu$ 3439, 2955, 2867, 1753, 1720 $cm^{-1}$; HRMS calcd. for $C_{22}H_{41}NSiBrO_5$(M+H): 506.1920, found: 506.1937; Anal. calcd. for $C_{22}H_{40}NSiBrO_5$: C 52.16, 7.96, found: C 52.28, 8.06.

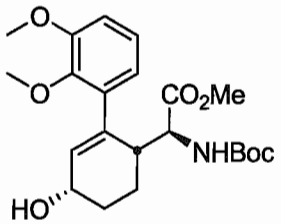
Procedure for recycling **331** to diastereomeric mixture **10**.

The undesired diastereomer of the C-ring fragment **331** (13.0 g, 6.4 mmol) was dissolved in DME (50 mL). DBU (0.49 g, 3.2 mmol) was added and the solution was brought to reflux and was stirred at reflux for 3 days. The mixture was then diluted with $Et_2O$ (100 mL) and washed with a 10 % citric acid solution to remove DBU, washed with brine (2 x 20 mL) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give diastereomeric mixture **10**. The mixture was then chromatographed as described above to give **9** and **331** (1:1 ratio) in 80 % combined yield.



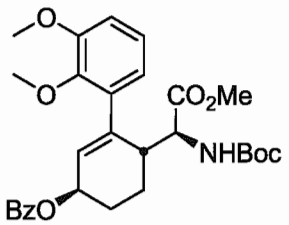

**7**

To a flame-dried flask containing $Pd(dppf)_2Cl_2$ (104 mg, 0.090 mmol) was added methyl ester **9** (456.4 mg, 0.901 mmol) in degassed THF (7 mL). Boronic acid **8** (328 mg, 1.802 mmol) was then added, along with $Cs_2CO_3$ (89 mg, 0.270 mmol). The resulting mixture was then stirred at reflux overnight. The reaction mixture was then filtered through a plug of silica with EtOAc, and concentrated to give 569 mg of brown oil. The oil was then chromatographed on $SiO_2$ using 4:1 hexanes : ethyl acetate as the eluent. The coupled product **7** (448 mg, 0.794 mmol, 88%) was obtained as a clear and colorless oil. $R_f$ 0.8 (1:1 Hex:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, $J$ = 7.91 Hz, 1H), 6.82 (dd, $J$ = 8.29, 1.1 Hz, 1H), 6.66 (d, $J$ = 7.65 Hz, 1H), 5.77 (dd, $J$ = 3.93, 1.54 Hz, 1H), 5.71 (d, $J$ = 9.72 Hz, 1H), 4.33 (dd, $J$ = 9.72, 2.28 Hz, 1H), 4.24 (m, 1H), 3.85 (s, 6H), 3.23 (s, 1H), 1.74 (m, 2H), 1.74 (q, $J$ = 6.86 Hz, 1H), 1.55 (bs, 4H), 1.42 (s, 9H), 0.91 (dd, $J$ = 6.84, 0.93 Hz, 6H), 0.85 (s, 7H), 0.10 (s, 6H) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 172.6, 155.2, 152.3, 146.2, 139.5, 134.6, 132.5, 124.1, 122.0, 111.8, 79.3, 63.4, 60.6, 55.7, 54.7, 52.1, 38.4, 34.4, 30.1, 28.4, 24.9, 20.5, 18.7, 17.9, -2.3, -2.8 ppm; IR (neat) $\nu$ 3449, 3019, 2956, 2401, 1748, 1716 cm$^{-1}$; LRMS (FAB + NBA matrix) *m/z* 404 (10.0), 375 (17.1), 287 (68.2), 227 (54.9); HRMS calcd. for $C_{30}H_{49}NO_7Si$: 506.2574, found: 506.2538.




**336**

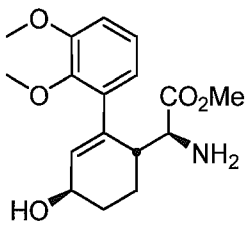
To a stirred solution of silyl ether **7** (448 mg, 0.794 mmol) in distilled THF (10 mL) was added tetra-*n*-butylammonium fluoride (0.87 mL, 0.873 mmol, 1M solution in THF) dropwise at 0 °C. The resulting solution was allowed to warm to r.t. and stir for 20 hrs. The reaction was diluted with distilled water (20 mL) and THF was removed under reduced pressure. The aqueous residue was then extracted with ethyl acetate (3x 10 mL). The combined organic layers were rinsed with distilled water (10 mL), brine (10 mL) and dried over sodium sulfate. The resulting mixture was filtered and concentrated to give free alcohol **336** (271 mg, 0.644 mmol, 81%) as a colorless oil. $R_f$ 0.3 (1:1 Hex:EtOAc); $[\alpha]_D^{20}$ 34.65 (c = 0.2, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.98 (t, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 5.89 (dd, *J* = 3.9, 1.40 Hz, 1H), 5.56 (d, *J* = 9.7 Hz, 1H), 4.3 (dd, *J* = 9.7, 2.5 Hz, 1H), 4.28 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.47 (q, *J* = 7.03, 1H), 3.37 (bs, 1H), 3.30 (s, 3H), 1.92 (m, 4H), 1.42 (s, 9H) ppm; $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 172.7, 155.2, 152.2, 146.1, 141.7, 134.4, 131.0, 124.0, 122.1, 112.0, 76.6, 63.5, 60.6, 55.8, 54.9, 52.1, 39.1, 30.0, 28.3, 18.8 ppm; IR (neat) *v* 3354, 3015, 2938, 1709, 1523 $cm^{-1}$; LRMS (EI) *m/z* 303 (13.4), 216 (100.0), 200 (24.3), 185 (8.7); HRMS calcd. for $C_{22}H_{31}NO_7$: 421.2101, found: 421.2077. Anal. calcd for $C_{22}H_{31}NO_7$: C 62.69, H 7.41, found: C 62.65, H 7.46.




**337**

To a stirred solution of alcohol **336** and benzoic acid in dry THF was added a solution of the Mitsunobu reagent, prepared by the addition of diethyl azodicarboxylate (DEAD) to

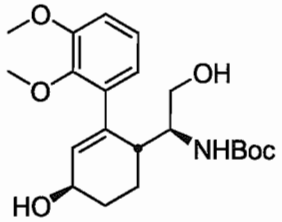
$PBu_3$ in THF at 0 °C. The reaction mixture was allowed to warm to room temperature over three hours and stirred for another three hours. The solvent was removed under reduced pressure and the resulting oil was chromatographed on silica gel (Hex: EtOAc 4:1). The pure product slowly solidified overnight in the freezer and was recrystallized from EtOAc. $R_f$ 0.27 (2:1 Hex:EtOAc); mp 102-105 °C (EtOAc); $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J*=7.2 Hz, 2H), 7.54 (t, *J*=7.4 Hz, 1H), 7.42 (t, *J*= 5.6 Hz, 2H), 6.98 (t, *J*= 7.9 Hz, 1H), 6.83 (dd, *J*= 1.5, 8.01 Hz, 1H) 6.70 (dd, *J*= 1.1, 7.2 Hz, 1H) 5.9 (s, 1H) 3.87 (s, 3H), 3.86 (s, 3H), 3.53 (s, 1H), 3.26 (s, 3H), 2.22 (m, 2H), 1.86 (m, 2H), 1.55 (s, 2H), 1.45 (s, 9H) ppm; $^{13}$C NMR ($CDCl_3$, 150 MHz) δ: 171.8, 166.3, 156.2, 152.8, 146.2, 139.2, 135.1, 133.0, 129.7, 128.4, 123.8, 122.2, 112.1, 61.4, 56.0, 51.8, 40.9, 28.5, 26.9, 24.8 ppm; LRMS (EI) *m/z* 525, 403 (8.4), 303 (20.8), 260 (50.4), 216 (100); HRMS calcd. for $C_{29}H_{35}NO_8$: 525.2363, found: 525.2369.




**339**

To a stirred solution of benzoyl ester **337** (148 mg, 0.282 mmol) in distilled DCM (1 mL) was added distilled TFA (0.25 mL) at r.t. The reaction was allowed to stir for 24 hr. and was then diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 3 mL). The aqueous layer was extracted with DCM (1 x 5 mL). Combined organic layers were rinsed with distilled water (5 mL) and brine (5 mL) and dried over $Na_2SO_4$. The organic layer was then filtered and concentrated to give a yellow oil. The crude mixture was purified by FCC (98:2 DCM:MeOH) to give **339** as a clear oil (33 mg, 0.103 mmol, 36%).

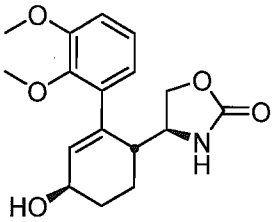
$R_f$ 0.3 (95:5 DCM:MeOH), $[\alpha]^{D}_{20}$ = 128.1 (c=0.29, $CHCl_3$, 95% CI); $^1$H NMR (300 MHz, $CDCl_3$) δ: 6.96 (t, *J*=7.94 Hz, 1H), 6.81 (d, *J*= 7.23 Hz, 1H), 6.65 (d, *J*= 7.53 Hz, 1H), 6.58 (d, *J*=5.13 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 4H), 3.46 (s, 3H), 3.40 (s, 1H), 3.40 (s, 1H), 2.30 (s, 1H), 2.01 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.41 (m, 1H), 1.25 (s, 1H), 0.86 (m, 1H) ppm; $^{13}$C NMR (150 MHz, $CDCl_3$) δ: 152.9, 146.8, 138.7, 134.4, 132.6, 124.0, 121.0, 111.6, 60.5, 58.5, 55.9, 52.1, 47.1, 38.8, 26.4, 23.1, 21.2, 14.3 ppm; *m/z* (EI) 303 (M - $H_2O$, 21.2) 272 (9.5) 244 (7.4) 216 (100) HRMS calcd for $C_{17}H_{23}NO_5$: 303.1471 (M+ -$H_2O$); found 303.1469 (M+ -$H_2O$)




**341**

Diester **337** (0.848 g, 1.6 mmol) was dissolved in 10 mL dry THF and cooled in an ice/water bath. Lithium aluminum hydride (0.153 g, 4.0 mmol) was added in one portion. The mixture was stirred for 2 hours warming to room temperature. The reaction was quenched by successively adding 0.15 mL water, 0.30 mL NaOH (15%), and 0.45 mL water. The aluminum salts were filtered off and the resulting oil was concentrated and chromatographed (1:2 Hex:EtOAc) yielding alcohol **341** (0.586 g, 1.5 mmol, 94 %) as a thick colorless oil. $R_f$ 0.26 (1:2 Hex:EtOAc); $[\alpha]^{20}_{D}$ 86.91 (MeOH); $^1$H NMR (DMSO *d*$^6$, 600 MHz) δ 6.89 (s, 2H), 6.54 (dd, *J* = 6.4, 1.8 Hz, 1H), 6.00 (d, *J* = 8.7 Hz, 1H), 5.56 (s, 1H), 4.70 (d, *J* = 5.3 Hz, 1H), 4.54 (t, *J* = 5.4 Hz, 1H), 4.18 (d, *J* = 3.7 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.16 (m, 4H), 1.97 (m, 1H), 1.74 (m, 1H), 1.32 (s, 9H), 1.12 (s, 2H) ppm; $^{13}$C NMR (DMSO *d*$^6$, 150 MHz) δ 155.5, 152.1, 146.0, 139.9, 136.6, 135.4, 124.0,

122.3, 111.7, 77.7, 66.0, 61.5, 60.2, 56.0, 53.0, 37.1, 32.0, 28.7, 20.2 ppm; IR (film) $\nu$ 3384, 2938, 1696, 1577, 1472 $cm^{-1}$; LRMS (EI) *m/z* 375 (m- $H_2O$), 321 (5.5), 264 (20.2), 244 (14.9), 216 (100.0); HRMS calcd. for $C_{21}H_{29}NO_5$: 375.2046, found: 375.2039. Anal. calcd. for $C_{21}H_{31}NO_6$ C 64.10, H 7.94, found: C 63.83, H 8.24.



**6**

To a solution of alcohol **341** (0.311 g, 0.79 mmol) in THF (10 mL) was added NaH (0.019 g, 0.79 mmol). The mixture was stirred at room temperature for 10 hours. The reaction was quenched with citric acid solution (10 % w/w, 5 mL). The aqueous phase was separated and extracted with ether (2x20 mL). The crude material (271 mg) was chromatographed on $SiO_2$ and chromatographed with 1:1 hexanes/ethyl acetate as the eluent. The product **6** (0.201 g, 0.63 mmol, 80 %) was isolated as a colorless oil.

$R_f$ 0.2 (1:2 Hex:EtOAc); $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.06 (t, $J$ = 7.92 Hz, 1H), 6.89 (d, $J$ = 8.22 Hz, 1H), 6.67 (dd, $J$ = 7.65, 1.17 Hz, 1H), 5.87 (m, 1H), 4.41 (m, 1H), 4.16 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.55 (t, $J$ = 4.74 Hz, 1H), 2.76 (bs, 1H), 2.27 (m, 1H), 1.67 (m, 1H), 1.59 (m, 1H), 1.40 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 159.3, 152.9, 145.7, 134.7, 124.8, 121.0, 111.7, 71.6, 71.1, 67.3, 67.0, 61.9, 61.4, 55.8, 53.3, 42.1, 31.7, 31.2, 19.3, 14.2 ppm; IR (neat) $\nu$ 3368, 2936, 1747, 1576 $cm^{-1}$; LRMS (EI) *m/z* 301 (3.9), 216 (49.1), 200 (14.1), 87 (87.3); HRMS calcd. for $C_{17}H_{21}NO_5$: 301.1314, found: 301.1310.

## 5.5 Biotransformations

### General procedure for small scale fermentation with *E. coli* JM109(pDTG601)

### Growth of colonies.

Agar plates consisted of bactotryptone (10 g/L), yeast extract (5 g/L), NaCl (5 g/L), agar (30 g/L), and ampicillin (100 mg/L). *E. coli* JM109(pDTG601) cells were streaked onto a plate and incubated at 35 °C for 24 hours. A single colony was isolated for the preculture preparations described in the following section.

### Preculture.

Luria Bertani (LB) media consisted of bactotryptone (10 g/L), yeast extract (5 g/L), NaCl (5 g/L), and ampicillin (100 mg/L). Three mL of LB media was inoculated with a single colony of *E. coli* JM109 (pDTG601) and grown at 35 °C in an orbital shaker.

### Fernbach shake flask.

Luria Bertani (LB) media consisted of bactotryptone (10 g/L), yeast extract (5 g/L), NaCl (5 g/L), and ampicillin (100 mg/L). A 3 L Fernbach shake flask was charged with 500 mL LB media and then inoculated with 1 mL of *E. coli* JM109(pDTG601) preculture media. The inoculum was grown for 12 hours at 35 °C in an orbital shaker. The contents of the shake flask were added to a 15 L Sartorius Biostat C fermentor and grown according to literature procedure for 24 hours.[156]

### Substrate addition

500 mL of cell broth was drained from the fermentor and the cells were separated by centrifugation. The supernatant was drained off and the cells were re-suspended in 500 mL phosphate buffer (0.1 M) containing 2 g/L glucose. The substrate (200-400 g/L) was

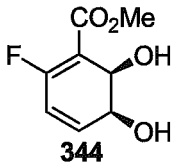
added neat or as a solution in isopropanol. Product formation was monitored by TLC (hexane/EtOAc, 1:1).

**Product isolation**

After 5 hours of incubation, the pH of the media was adjusted to 8.5 with NaOH (1 M) and the supernatant was separated from the cells by centrifugation. The supernatant was then extracted with EtOAc (3x500 mL). The extract was washed with saturated $Na_2CO_3$ (100 mL) and brine (100 mL) and dried over anhydrous $Na_2SO_4$. Ethyl acetate was removed under reduced pressure and the crude material was purified by crystallization (EtOAc/pentane) or flash colum chromatography.

**Large scale fermentations**

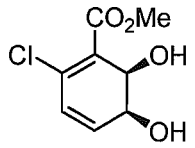
Large scale fermentations were performed according to literature procedure.[156]




**344**

**methyl 2-fluoro-5,6-dihydroxycyclohexa-1,3-dienecarboxylate (344)**:

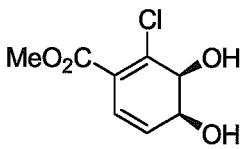
$R_f$ 0.15 (1:1 Hex:EtOAc); mp 74-76 °C (EtOAc); $[\alpha]^D_{20}$ = +73.2 (c 1.05, MeOH); $^1$H NMR ($CDCl_3$, 600 MHz) δ 6.33 (m, 1H), 5.94 (ddd, $J$ = 10.2, 8.3, 2.6 Hz, 1H), 4.71 (t, $J$ = 6.2 Hz, 1H), 4.55 (m, 1H), 3.83 (s, 3H), 3.17 (bs, 1H), 3.09 (brs, 1H) ppm; $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 166.0 (d, $J$ = 2.2 Hz), 163.2 (d, $J$ = 281.0 Hz), 143.1 (d, $J$ = 12.1 Hz), 119.6 (d, $J$ = 36.2 Hz), 106.2 (d, $J$ = 2.2 Hz), 69.0, 67.0 (d, $J$ = 6.6 Hz), 52.2 ppm; $^{19}$F NMR ($CDCl_3$, 282 MHz) δ -92.6 (s) ppm; IR (film) 3558, 3025, 1694, 1439, 1401, 1040 cm$^{-1}$; LRMS (EI) *m/z* 188 (15), 133 (44), 119 (49), 102 (100), 91 (37), 90 (46), 86 (28), 74 (16), 46 (27); HRMS calcd. for $C_8H_9FO_4$ ($M^+$): 188.0485, found: 188.0484; Anal. calcd. for $C_8H_9FO_4$: C, 51.07; H, 4.82, found: C, 51.18; H, 4.76.




**348**

**methyl 2-chloro-5,6-dihydroxycyclohexa-1,3-dienecarboxylate (348)**:

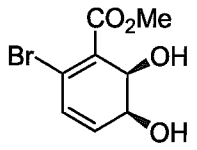
$R_f$ 0.25 (1:1 Hex:EtOAc); mp 107-109 °C (EtOAc); $[\alpha]^D_{20}$ = +86.6 (c 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 600 MHz) δ 6.35 (d, $J$ = 9.8 Hz, 1H), 6.03 (dd, $J$ = 9.8, 3.0 Hz, 1H), 4.44 (m, 1H), 4.31 (d, $J$ = 6.0 Hz, 1H), 3.83 (s, 3H), 2.50 (bs, 2H) ppm; $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 164.8, 140.5, 127.8, 125.1, 124.0, 72.5, 67.4, 52.3 ppm; IR (KBr) 3422, 2959, 1721, 1578, 1444, 1270, 758 $cm^{-1}$; LRMS (EI) *m/z* $[M-H_2O]^+$: 188 (15), 186 (43), 157 (32), 155 (100), 99 (14); HRMS calcd. for $C_8H_9ClO_4$ $[M-H_2O]^+$: 188.0084, found: 188.0077.




**349**

**methyl 2-chloro-3,4-dihydroxycyclohexa-1,5-dienecarboxylate (349)**:

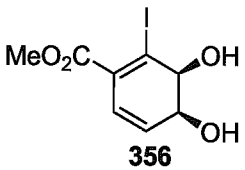
$R_f$ 0.18 (1:1 Hex:EtOAc); mp 107-109 °C (pentane–ethyl acetate); $[\alpha]_D{}^{20}$ = +36.9 (c 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.18 (ddd, $J$ = 10.0, 2.4, 1.2 Hz, 1H), 6.01 (dd, $J$ = 10.0, 2.4 Hz, 1H), 4.64 (ddd, $J$ = 6.0, 4.7, 1.2 Hz, 1H), 4.52 (ddt, $J$ = 8.7, 6.0, 2.4 Hz, 1H), 3.86 (s, 3H), 2.76 (d, $J$ = 9.6 Hz, 1H), 2.60 (d, $J$ = 4.7 Hz, 1H) ppm; $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 166.3, 138.8, 138.5, 127.5, 123.8, 68.6, 67.7, 52.3 ppm; IR (KBr) 3398, 3459, 1698, 1317, 1057, 762 $cm^{-1}$; LRMS (EI) *m/z*: 204 (14), 173 (23), 172 (54), 155 (50), 146 (32), 145 (36), 144 (100), 143 (80), 139 (27), 99 (27), 81 (41), 53 (25), 51 (21); HRMS calcd. for $C_8H_9ClO_4$: 204.0189, found: 204. 0190.




**352**

**methyl 2-bromo-5,6-dihydroxycyclohexa-1,3-dienecarboxylate (352)**:

$R_f$ 0.18 (1:1 Hex:EtOAc); mp 106-109 °C ($CHCl_3$); $^1$H NMR ($CDCl_3$, 600 MHz) δ 6.17 (dd, $J$ = 10.0, 2.5 Hz, 1H), 6.04 (ddd, $J$ = 10.0, 2.5, 1.3 Hz, 1H), 4.57 (m, 1H), 4.49 (m, 1H), 3.85 (s, 3H), 3.00 (d, $J$ = 7.9 Hz, 1H), 2.97 (bs, 1H) ppm; $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 166.6, 137.5, 130.0, 128.0, 127.3, 68.4, 68.1, 52.3 ppm; IR (KBr) 3402, 1703, 1437, 1314, 1234, 1048 cm$^{-1}$; LRMS *m/z*: 248 (9), 218 (38), 216 (47), 190 (82), 189 (53), 188 (85), 187 (48), 109 (71), 108 (31), 81 (100), 65 (79), 59 (45), 53 (54); HRMS calcd. for $C_8H_9BrO_4$: 247.9684, found: 247.9679.



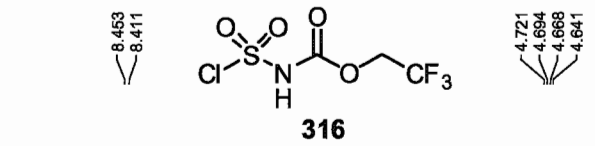

**356**

**methyl 3,4-dihydroxy-2-iodocyclohexa-1,5-dienecarboxylate (356)**:

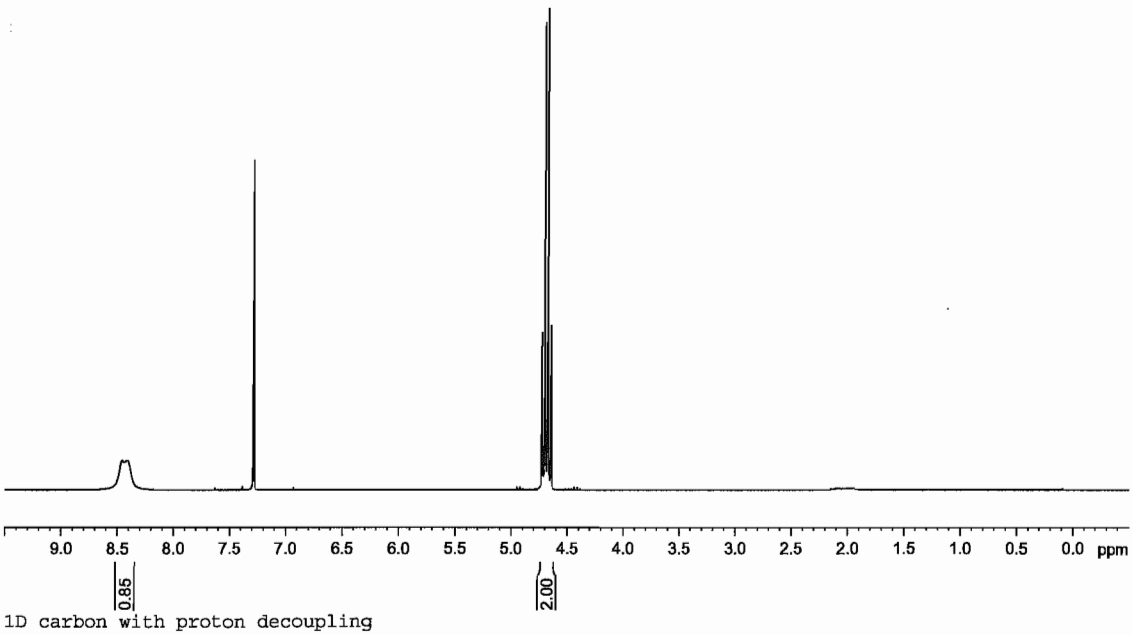
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.19 (d, $J$ = 9.8 Hz, 1H), 6.11 (dd, $J$ = 9.8, 3.8 Hz, 1H), 4.42 (m, 1H), 4.36 (t, $J$ = 6.6 Hz, 1H), 3.83 (s, 3H), 3.12 (brd, $J$ = 7.6 Hz, 1H), 2.59 (brd, $J$ = 7.2 Hz, 1H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$) δ 166.0, 134.3, 129.3, 123.9, 111.20, 67.2, 52.4 ppm; LRMS I: 296 (12), 278 (83), 264 (38), 247 (90), 231 (31), 137 (100), 109 (95), 92 (43), 81 (89), 63 (35), 59 (38), 53 (62); HRMS calcd for $C_8H_9IO_4$: 295.9546, found: 295.9538.

# 6 Selected Spectra

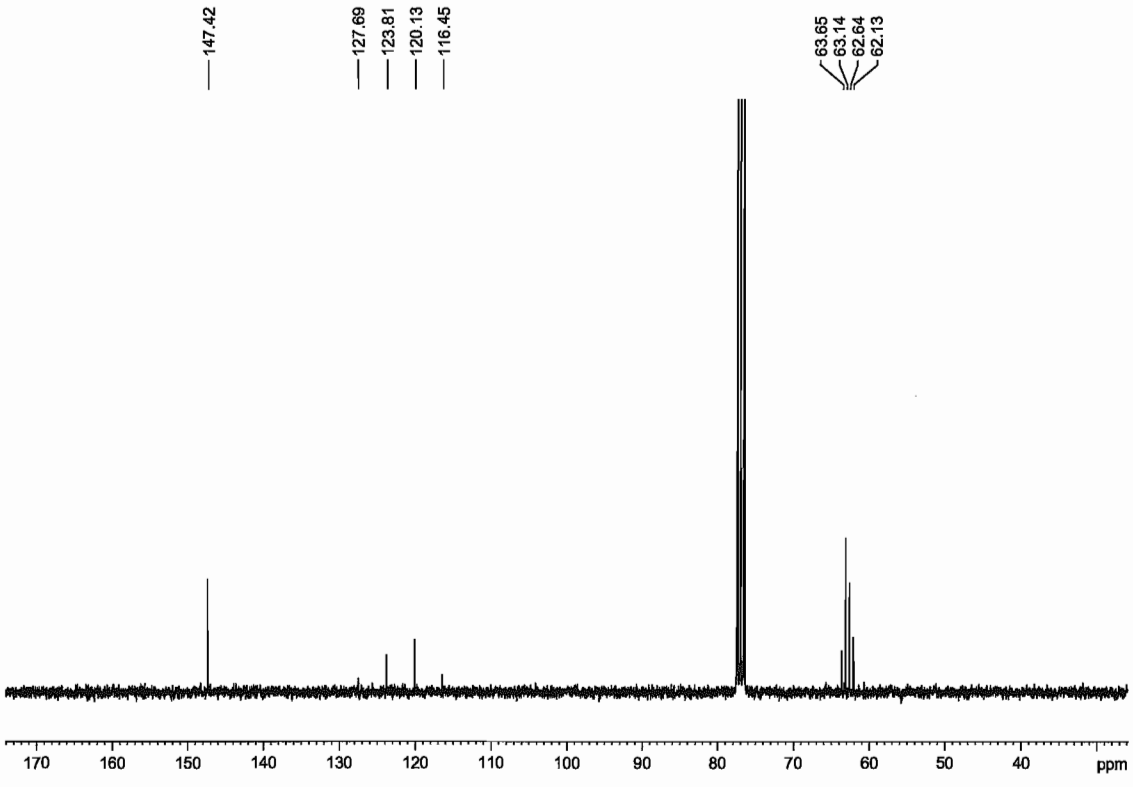
1D proton



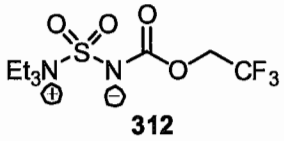

316




1D carbon with proton decoupling



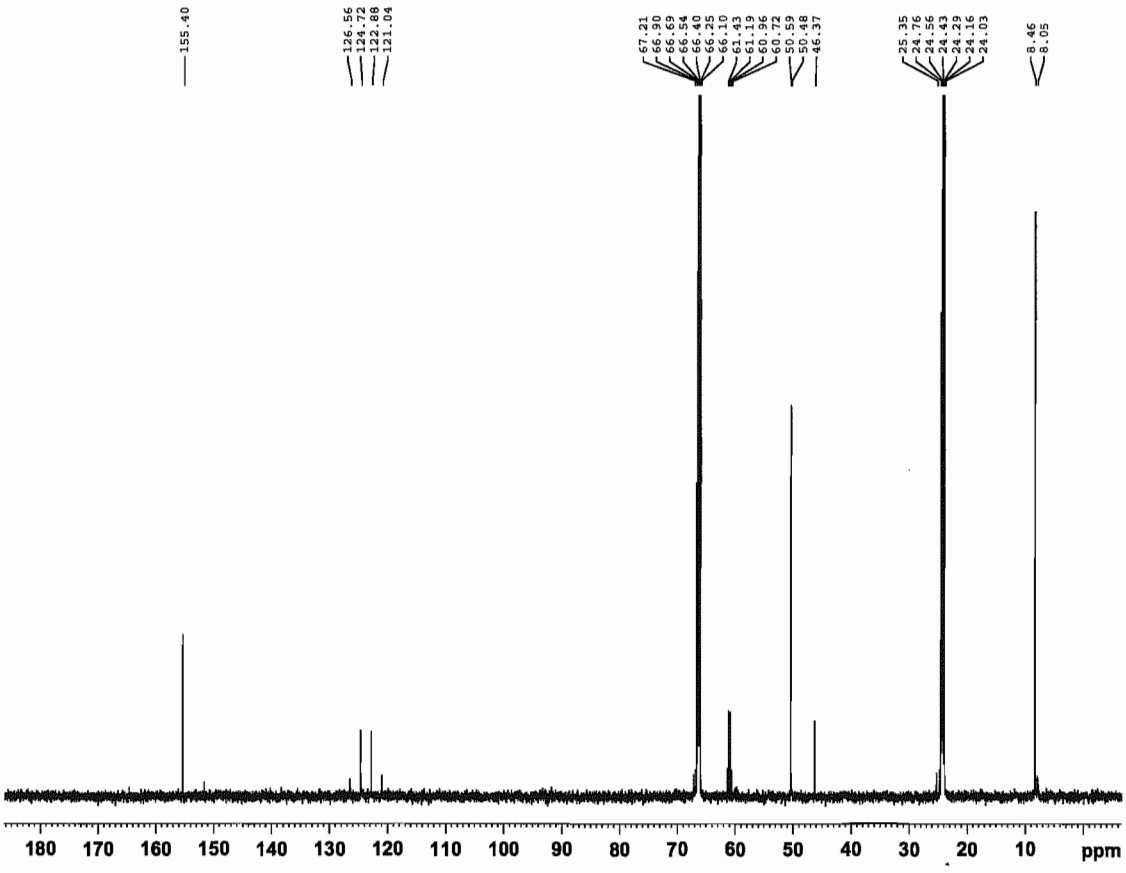
1D proton



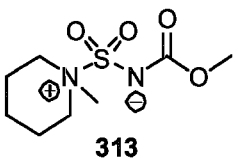
312




1d carbon with proton decoupling



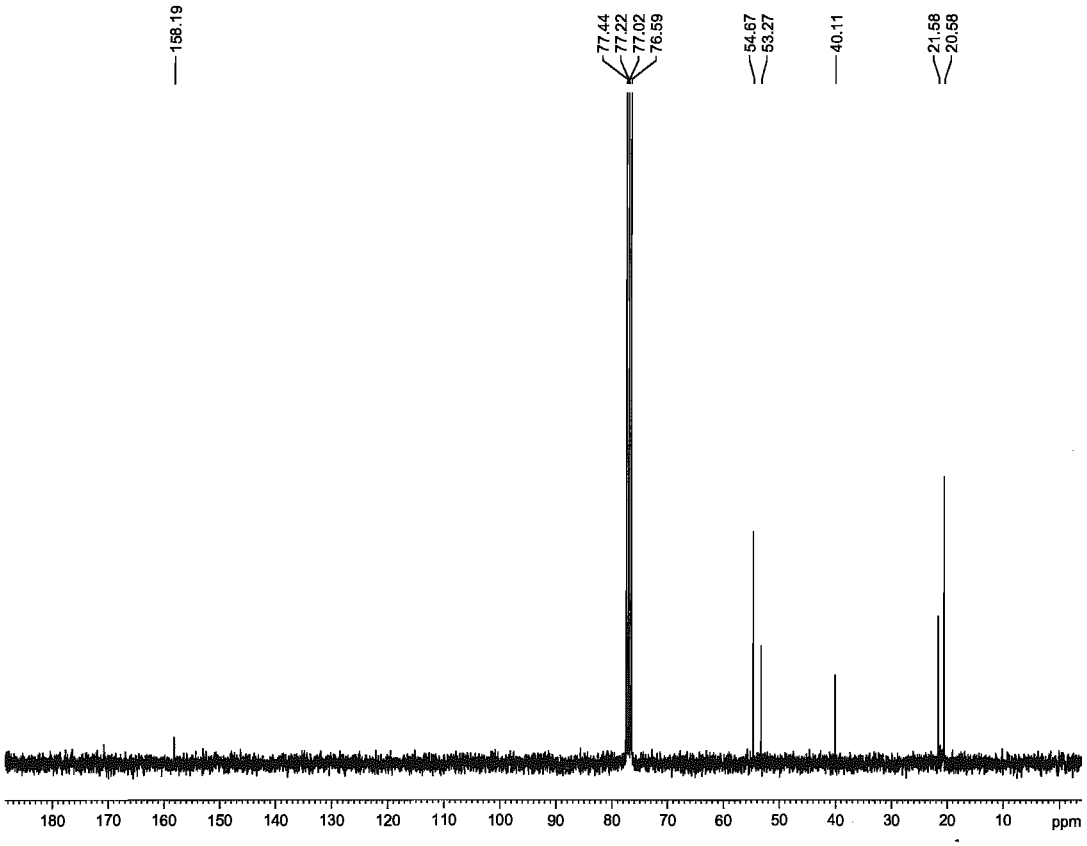
1D proton



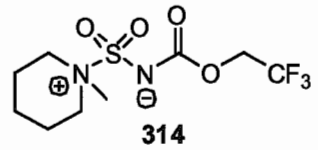
313




1D carbon with proton decoupling



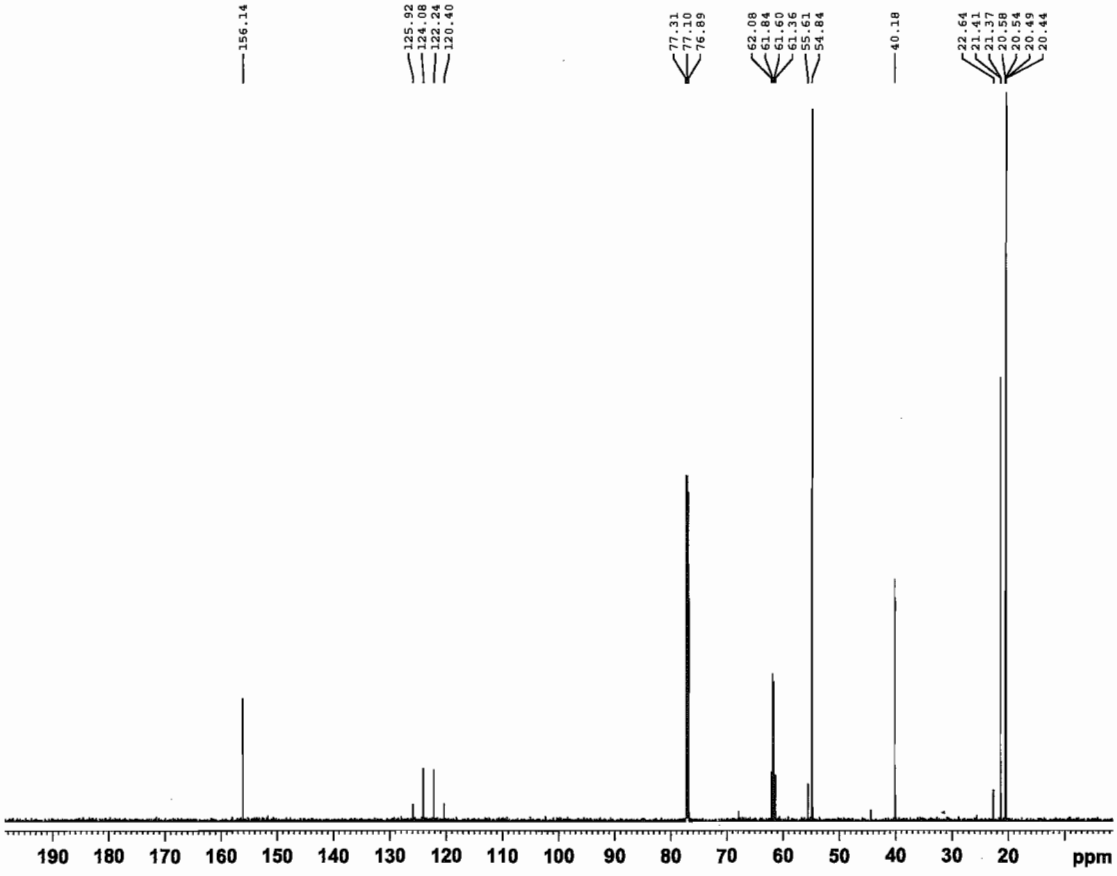
1D proton



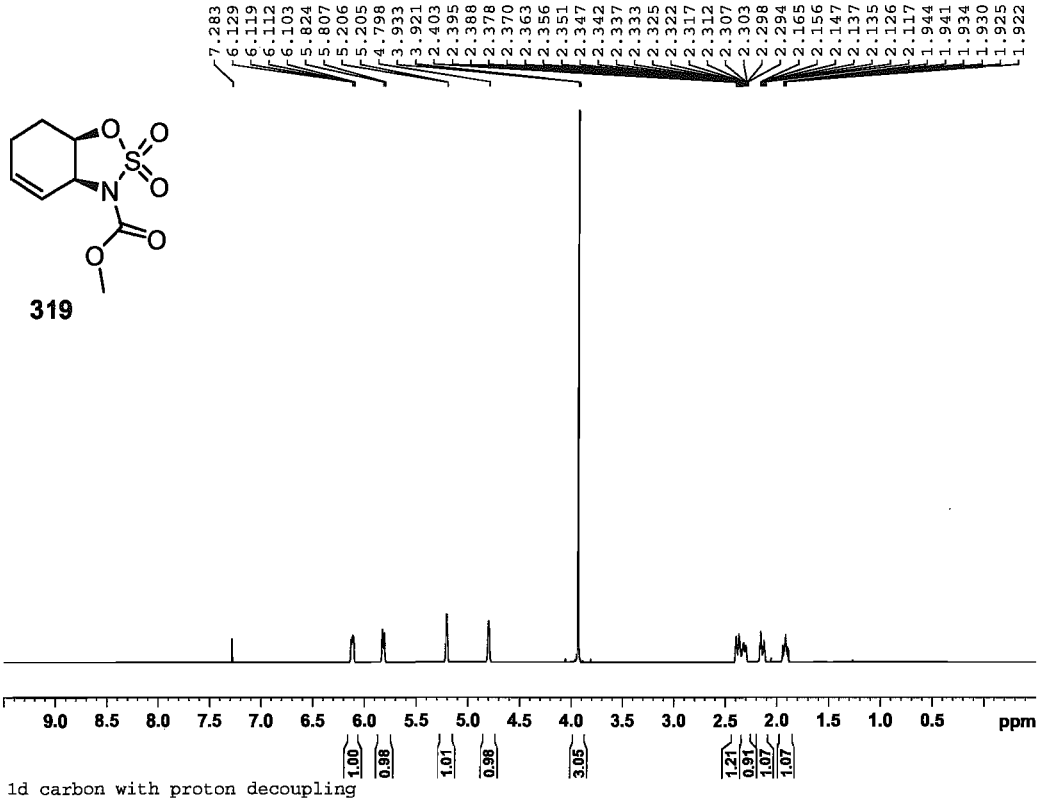
**314**



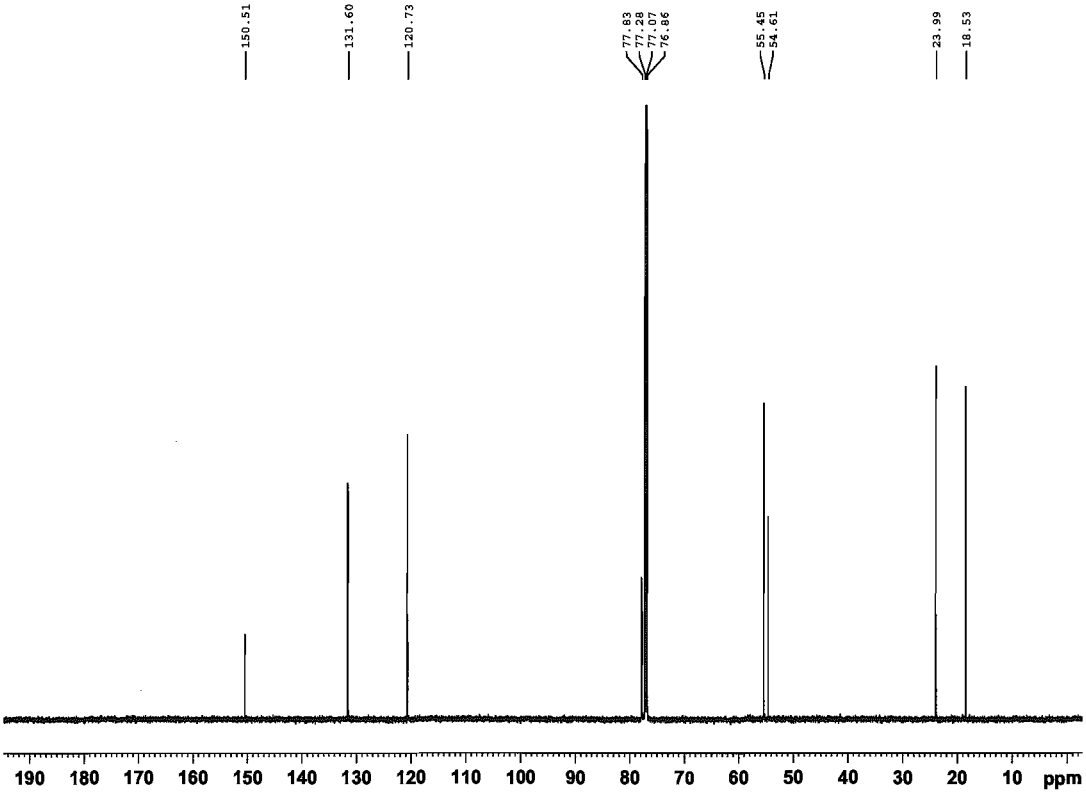

1d carbon with proton decoupling



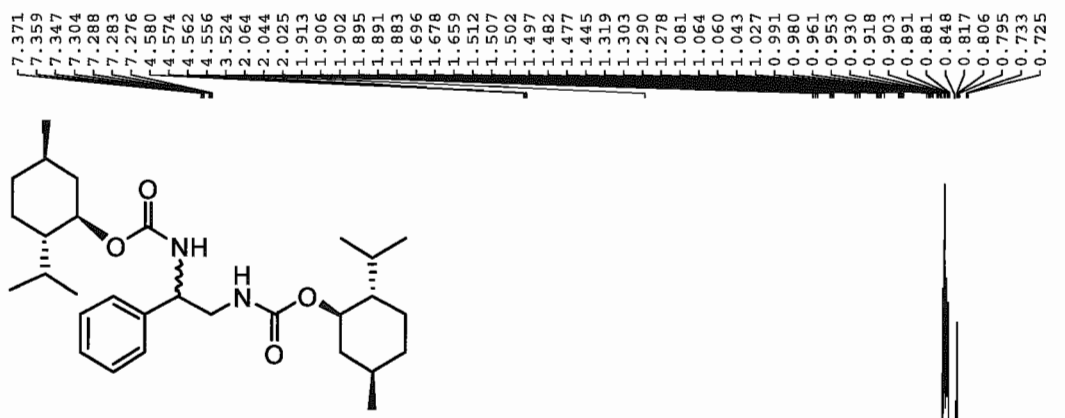
1d proton




1d carbon with proton decoupling



1d proton

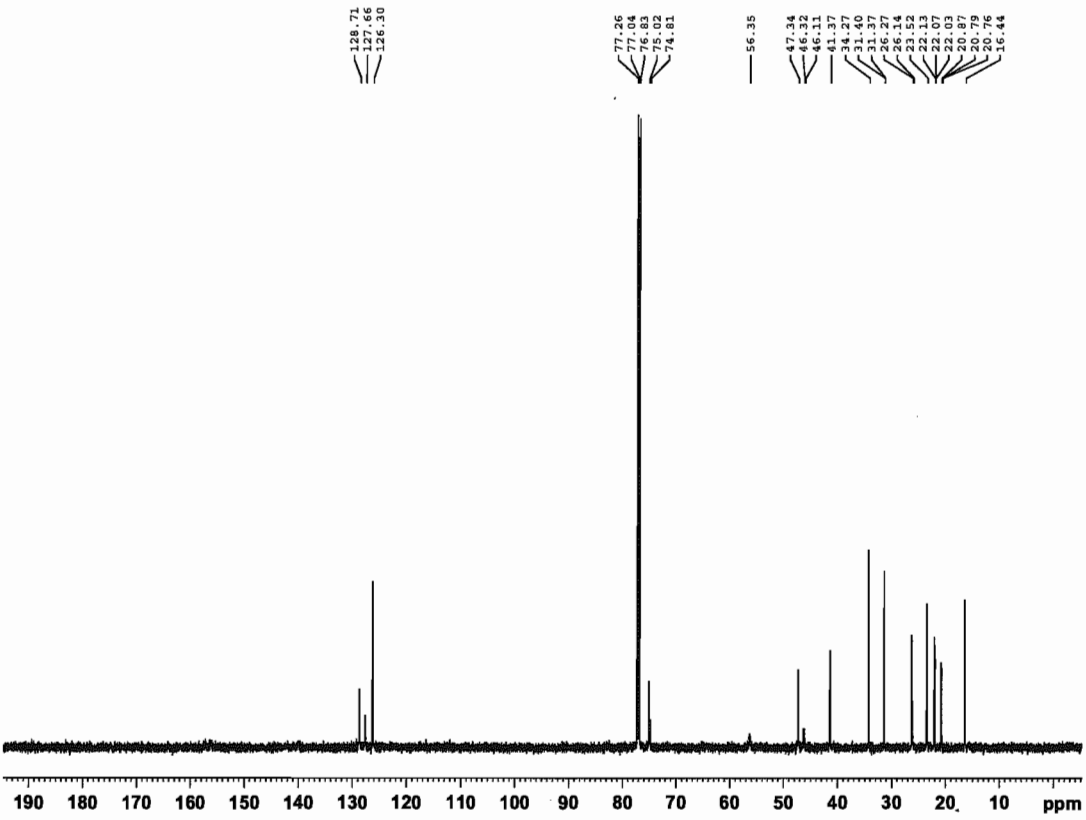




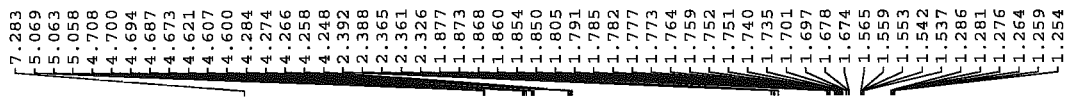
322

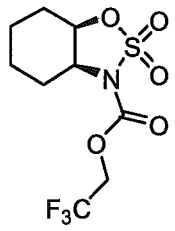



1d carbon with proton decoupling



1d proton

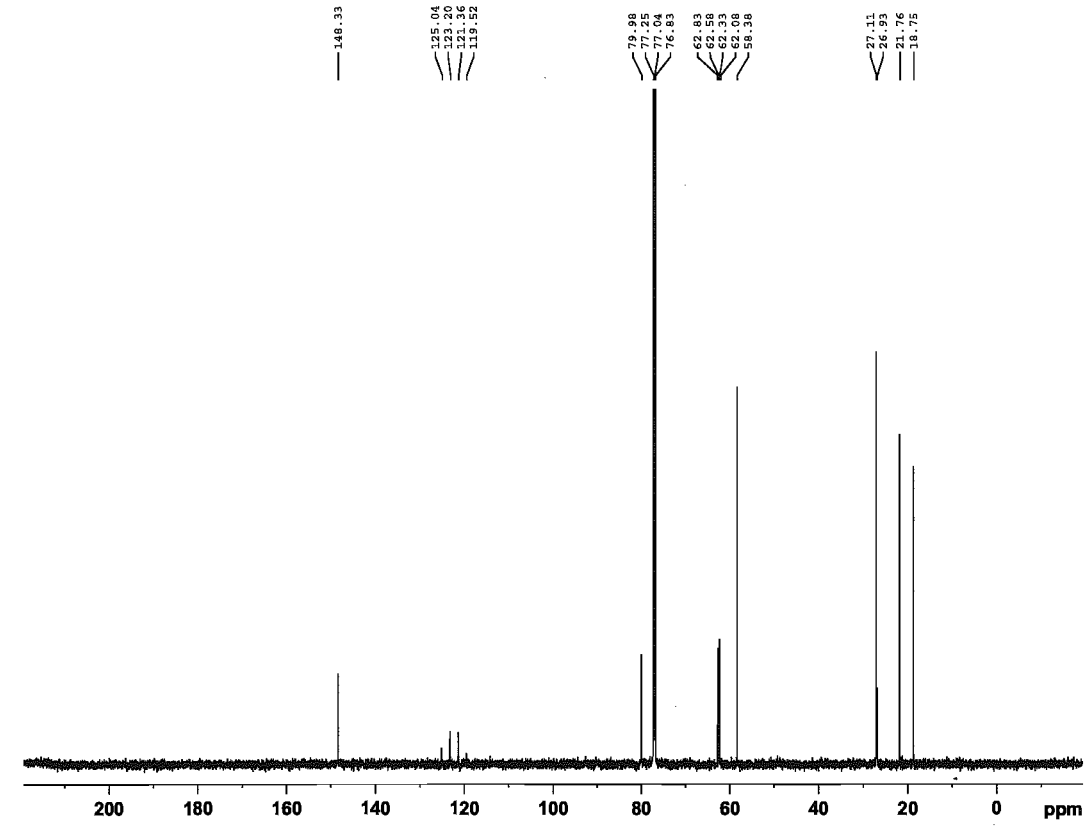


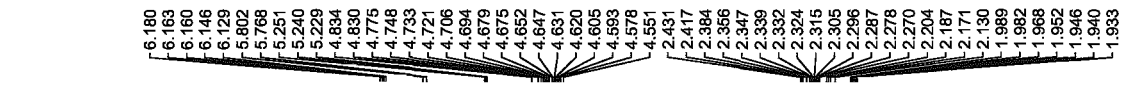

**323**

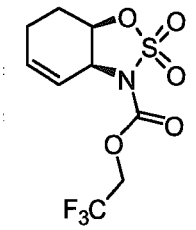



1d carbon with proton decoupling

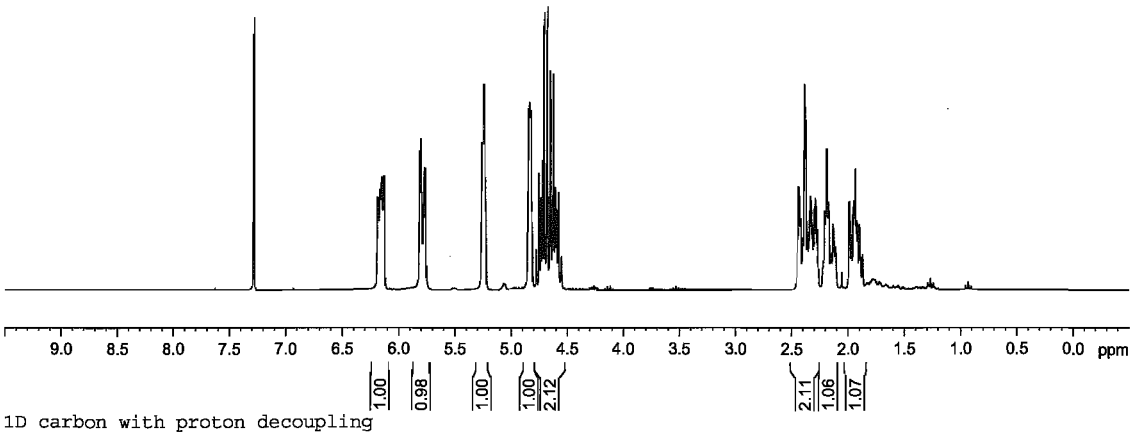


1D proton

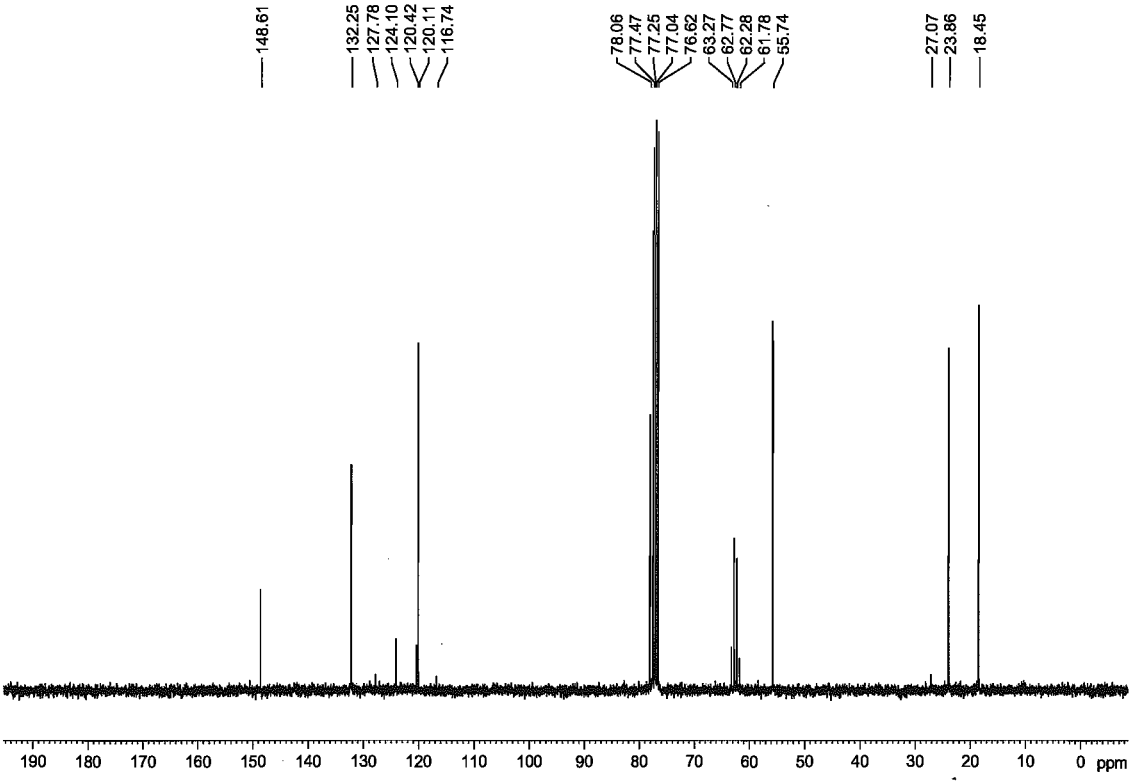


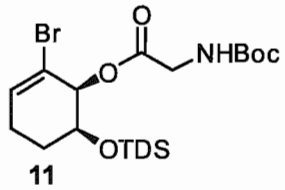

**324**




1D carbon with proton decoupling



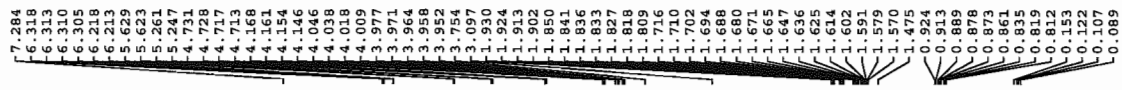
1D proton

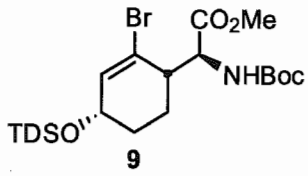

Br
O
NHBoc
O
OTDS

**11**


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.00
0.81
2.98
1.03
1.14
2.62
2.36
9.44
2.82
2.18
13.94
6.17

1d proton

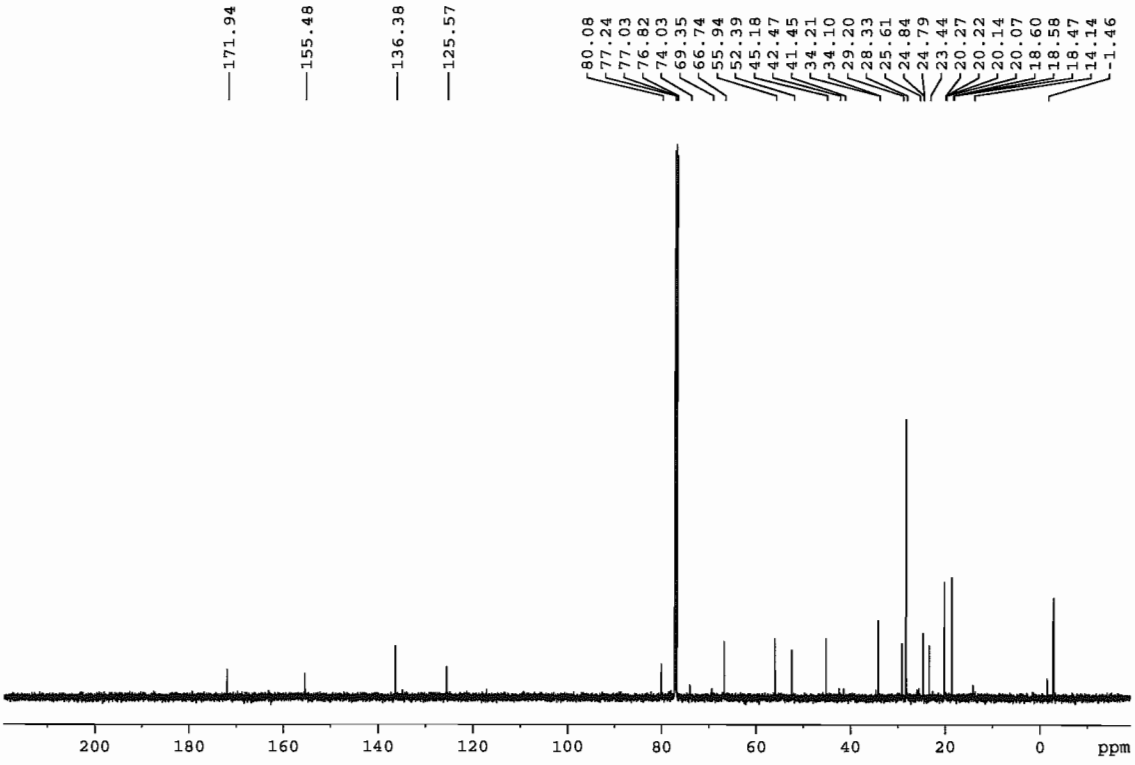




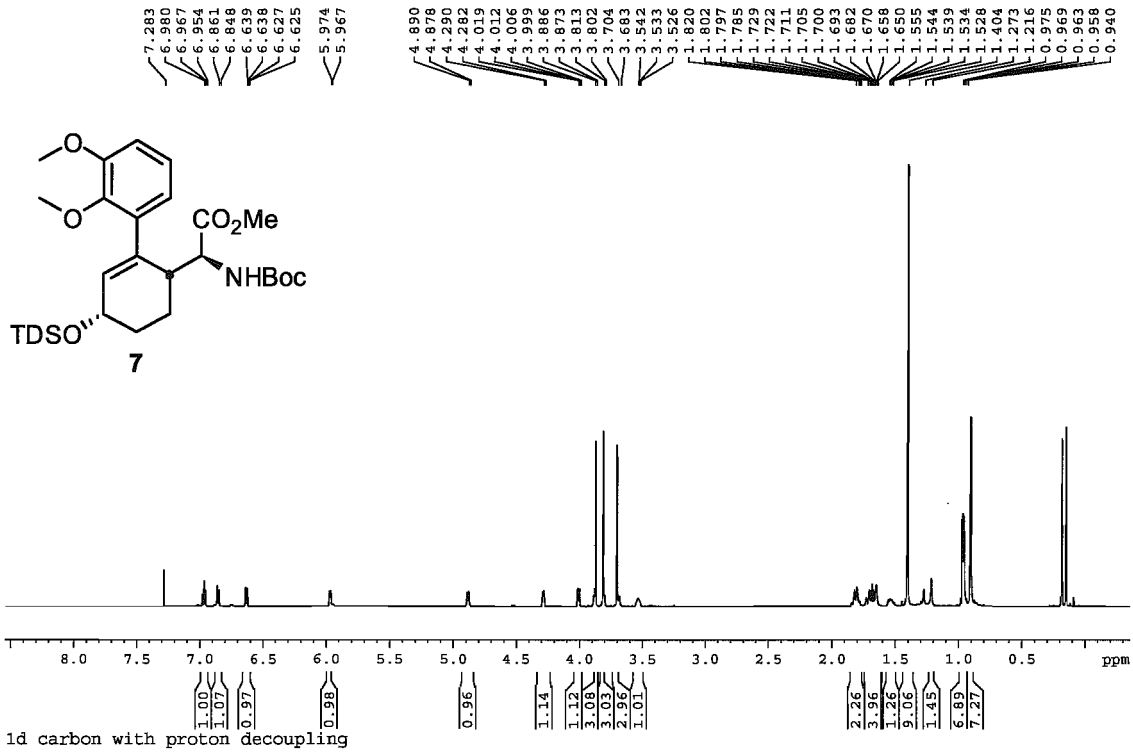




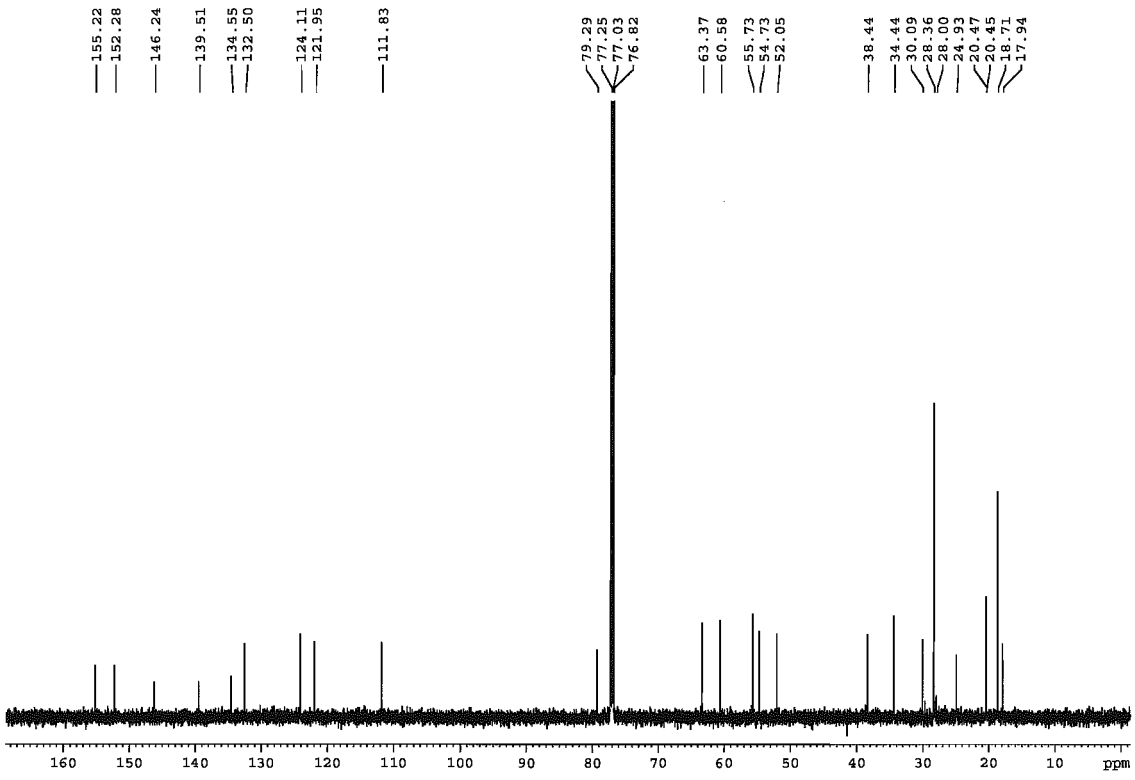
1d carbon with proton decoupling



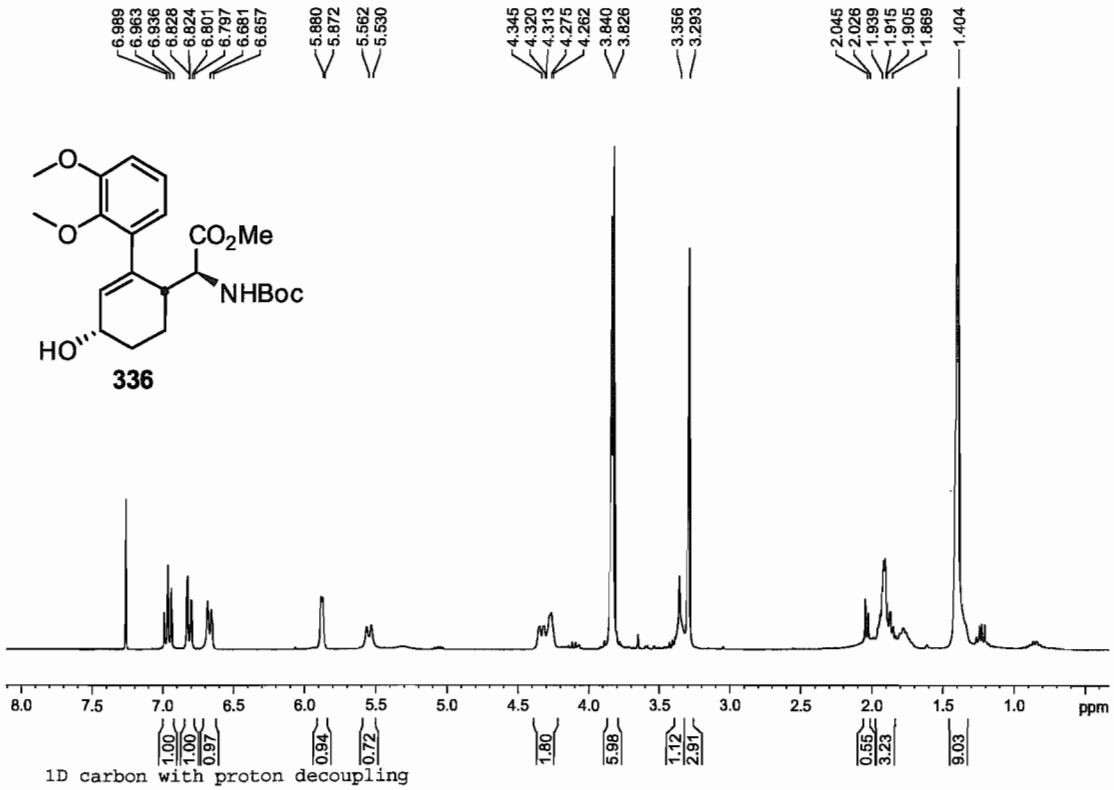
1d proton



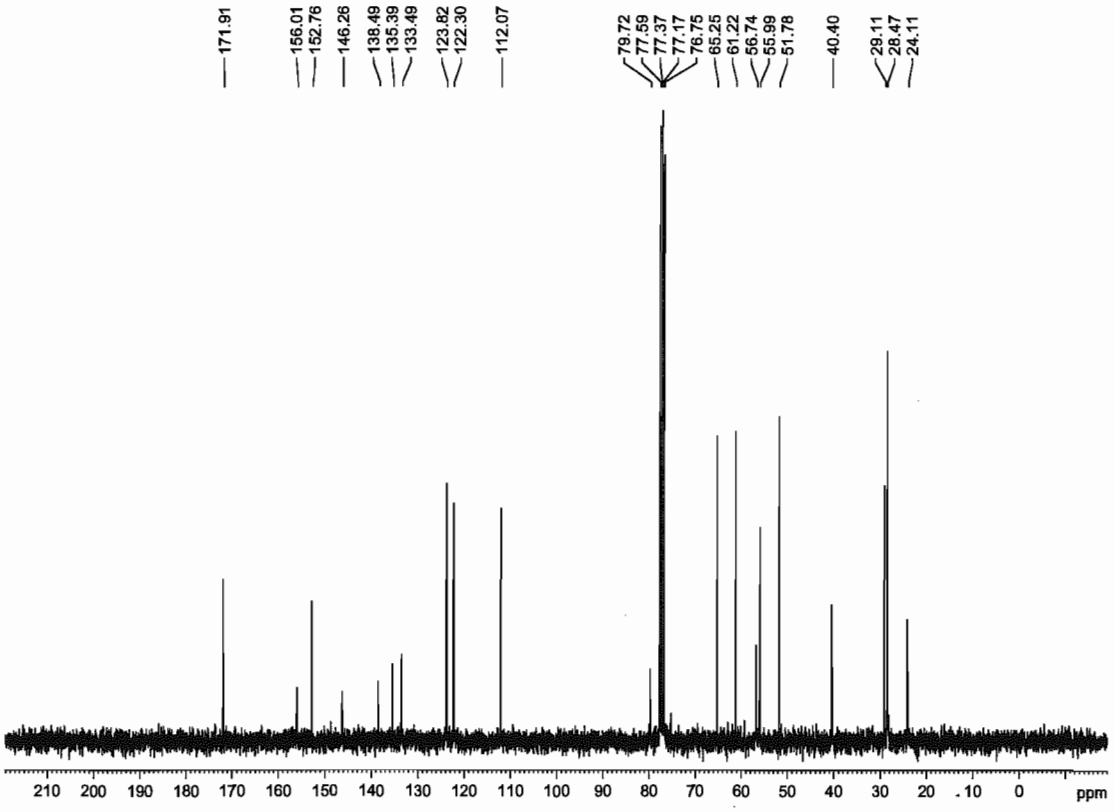

1d carbon with proton decoupling



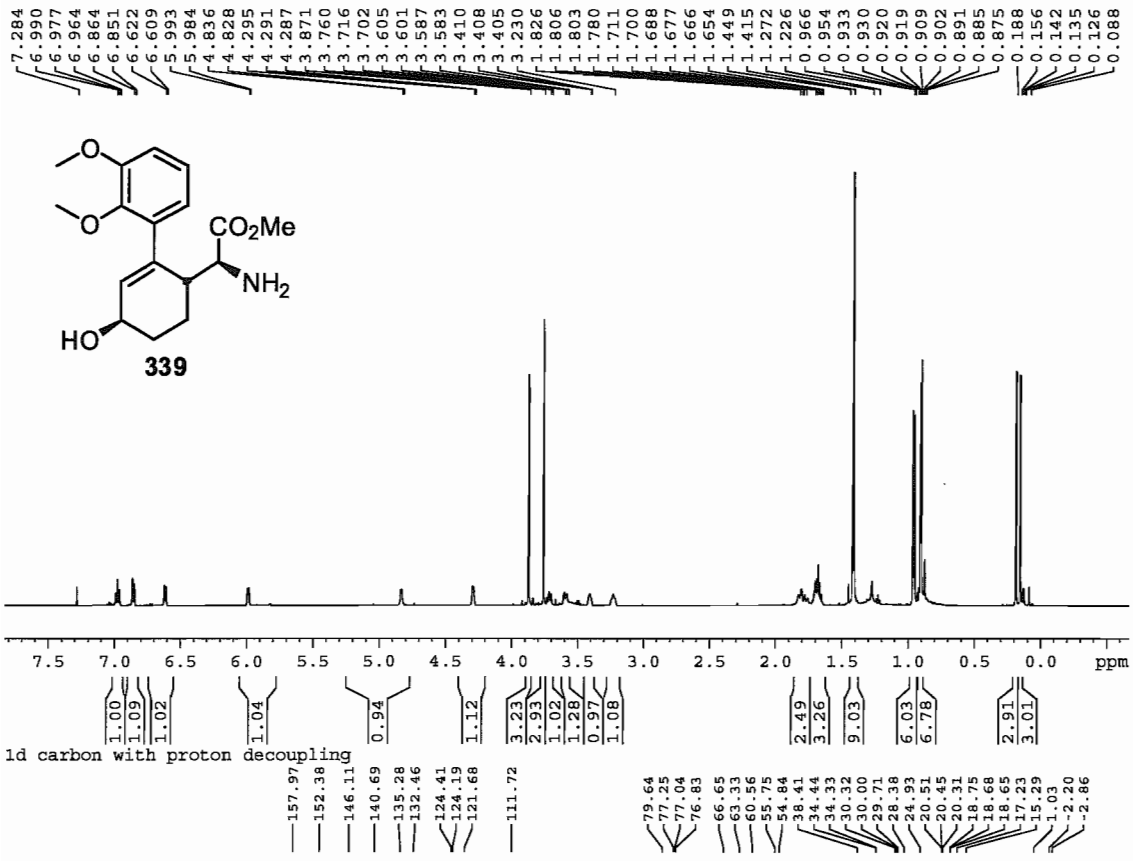
1D proton



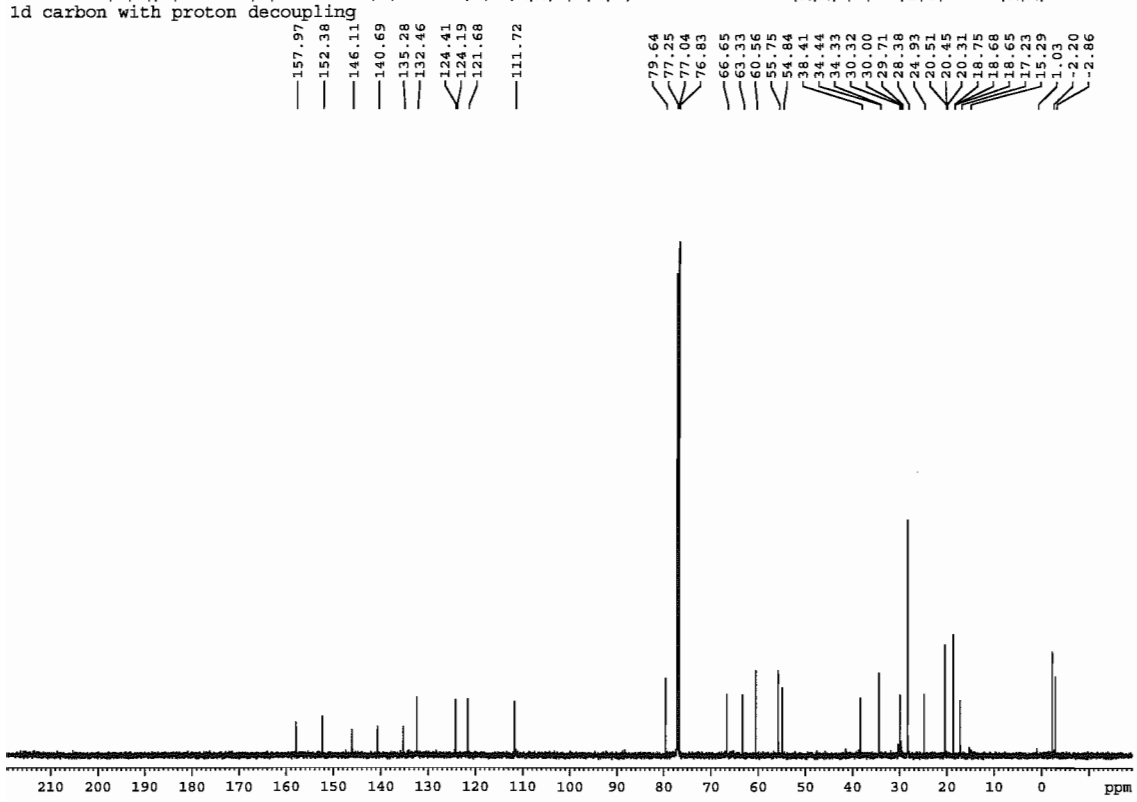

1D carbon with proton decoupling



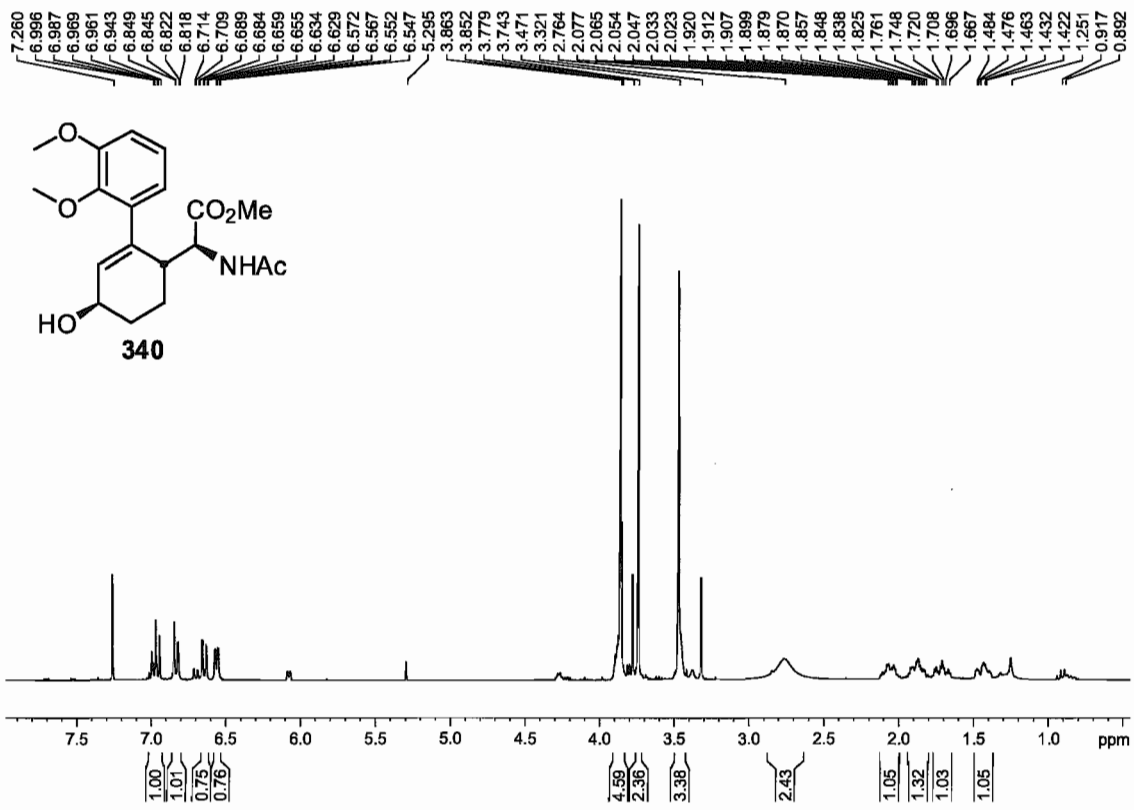
1d proton




1d carbon with proton decoupling

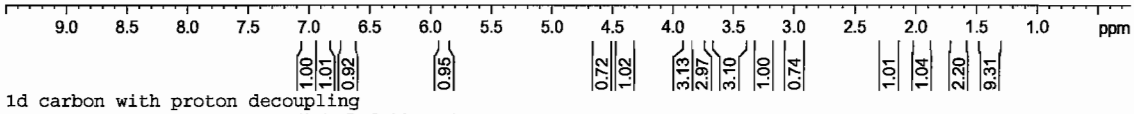


1D proton

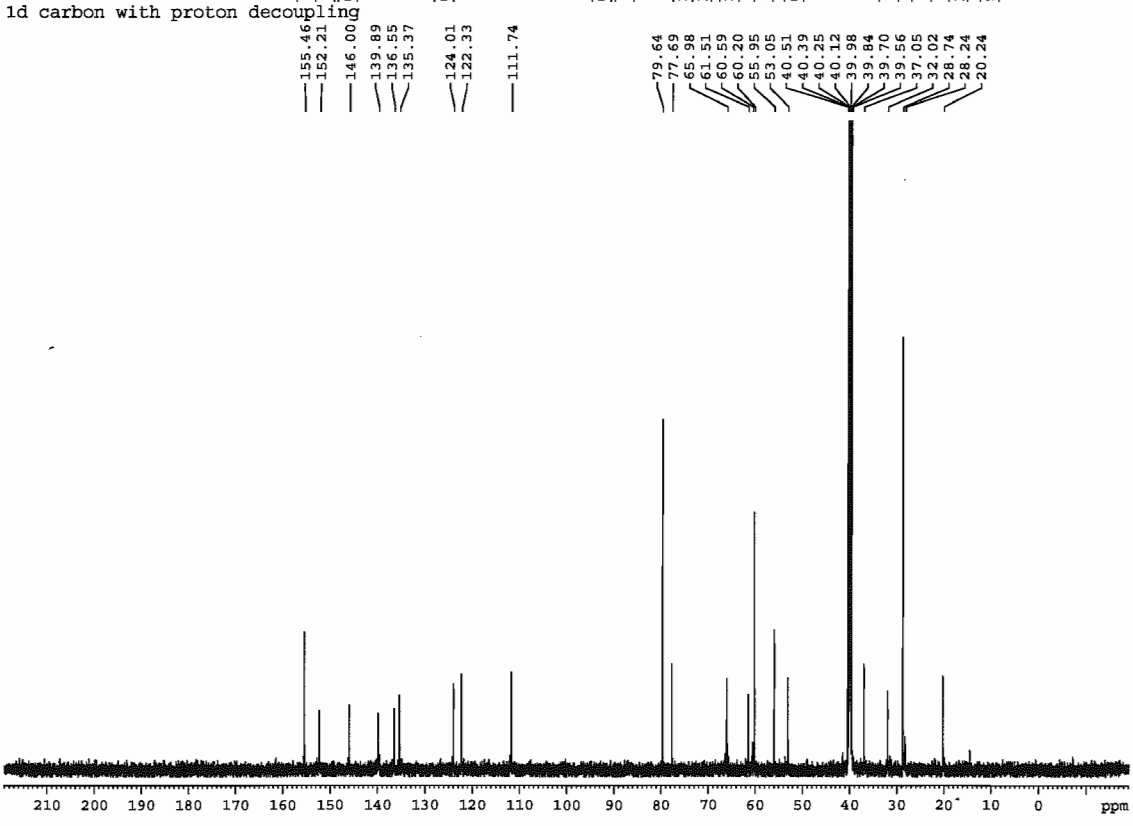

7.260
6.996
6.987
6.969
6.961
6.943
6.849
6.845
6.822
6.818
6.714
6.709
6.689
6.684
6.659
6.655
6.634
6.629
6.572
6.567
6.552
6.547
5.295
3.863
3.852
3.779
3.743
3.471
3.321
2.764
2.077
2.065
2.054
2.047
2.033
2.023
1.920
1.912
1.907
1.899
1.879
1.870
1.857
1.848
1.838
1.825
1.761
1.748
1.720
1.708
1.696
1.667
1.484
1.476
1.463
1.432
1.422
1.251
0.917
0.892
O
O
CO2Me
NHAc
HO
340
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.01
0.75
0.76
4.59
2.36
3.38
2.43
1.05
1.32
1.03
1.05

1D proton

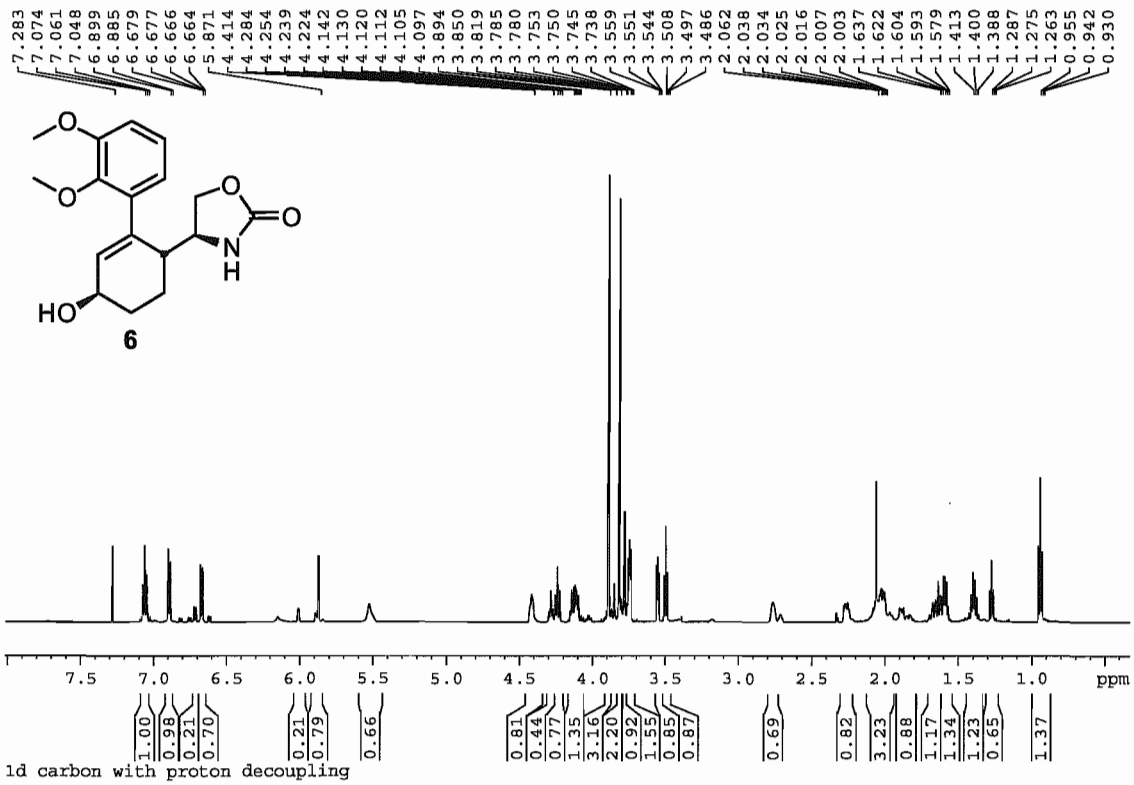

**341**



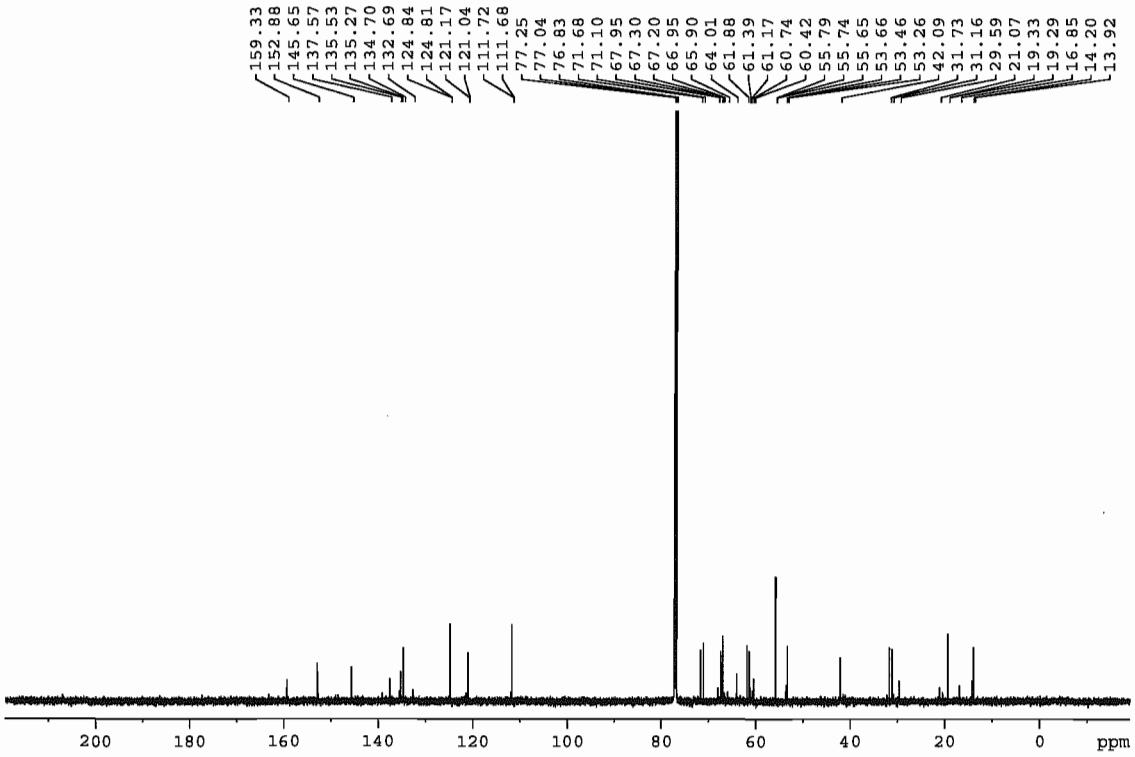

1d carbon with proton decoupling



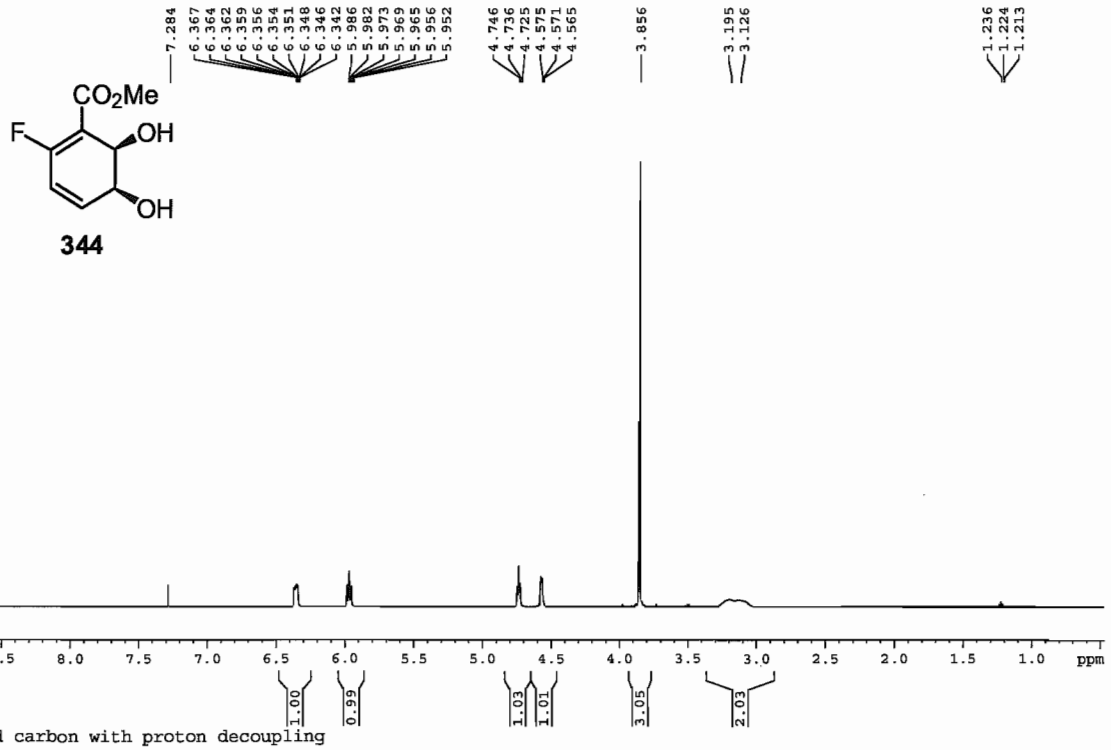
1d proton



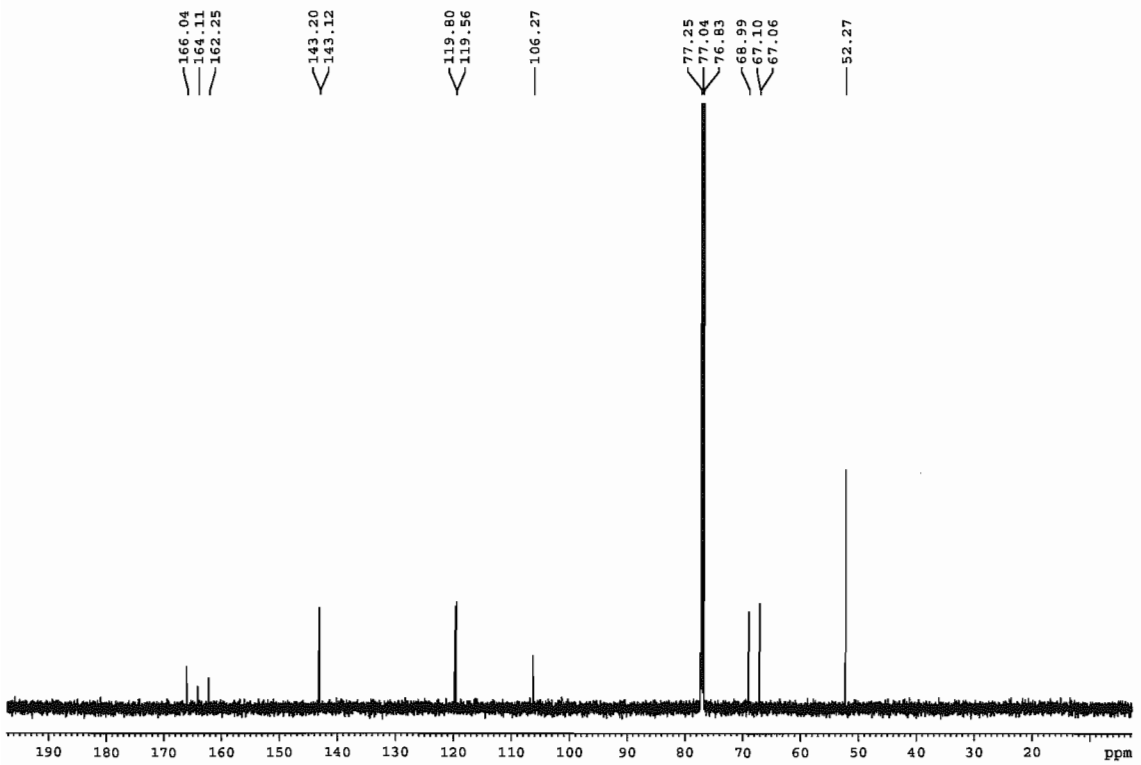

1d carbon with proton decoupling



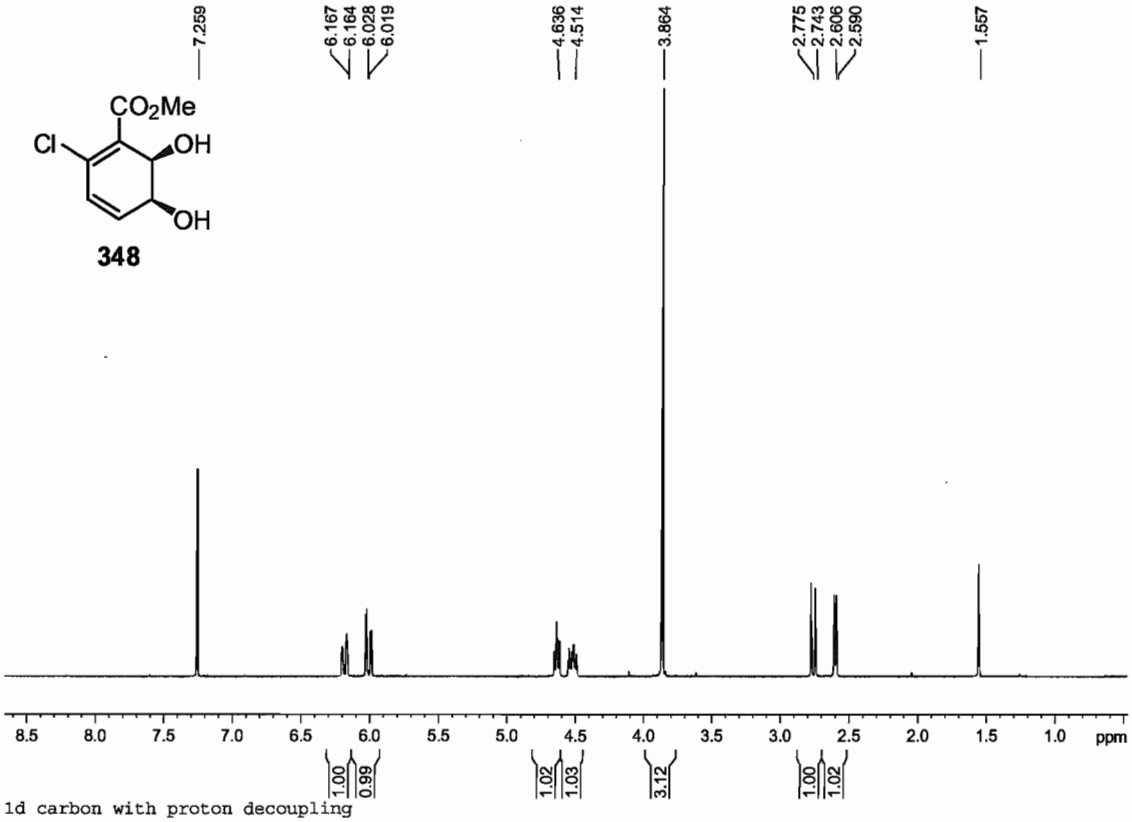
1d proton



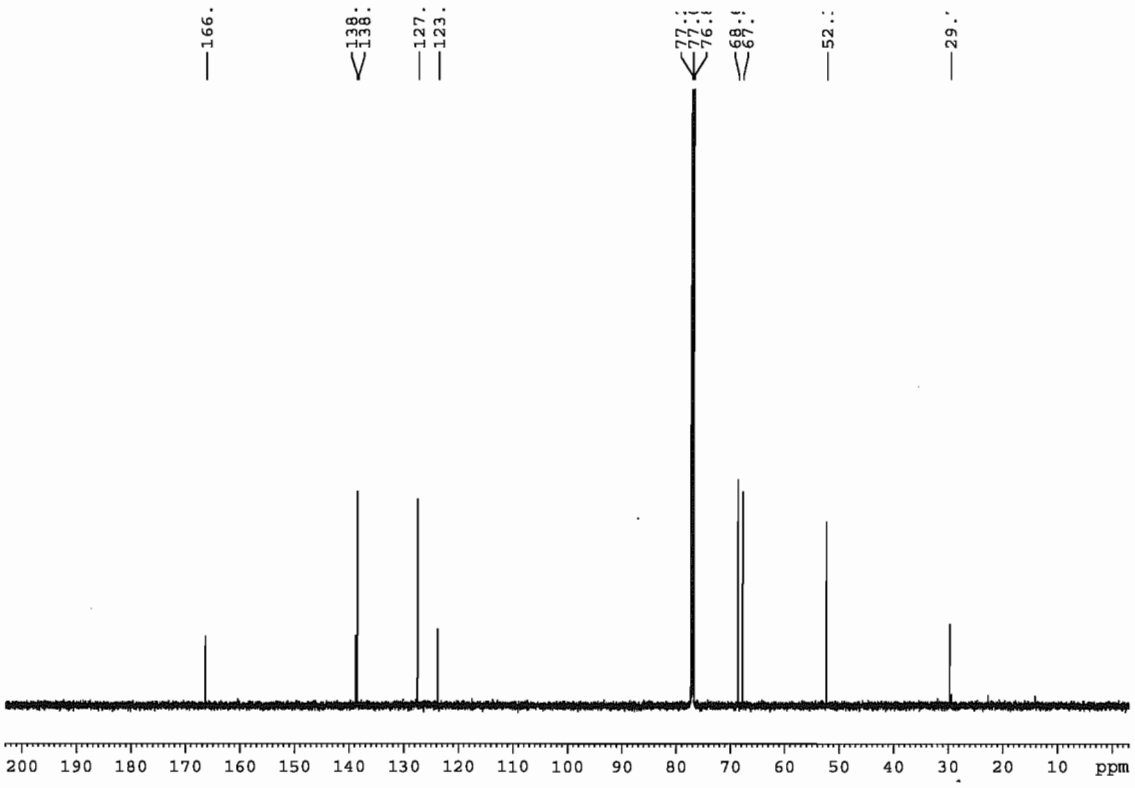

1d carbon with proton decoupling



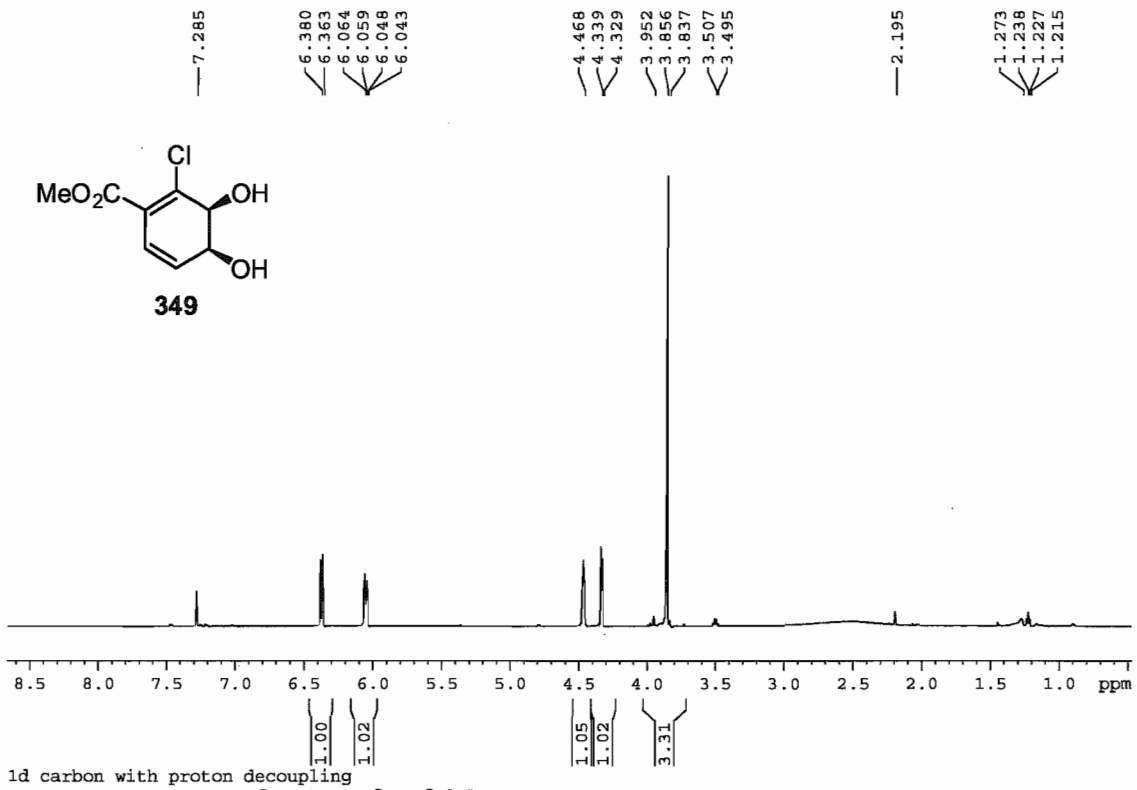
1D proton




1d carbon with proton decoupling



1d proton

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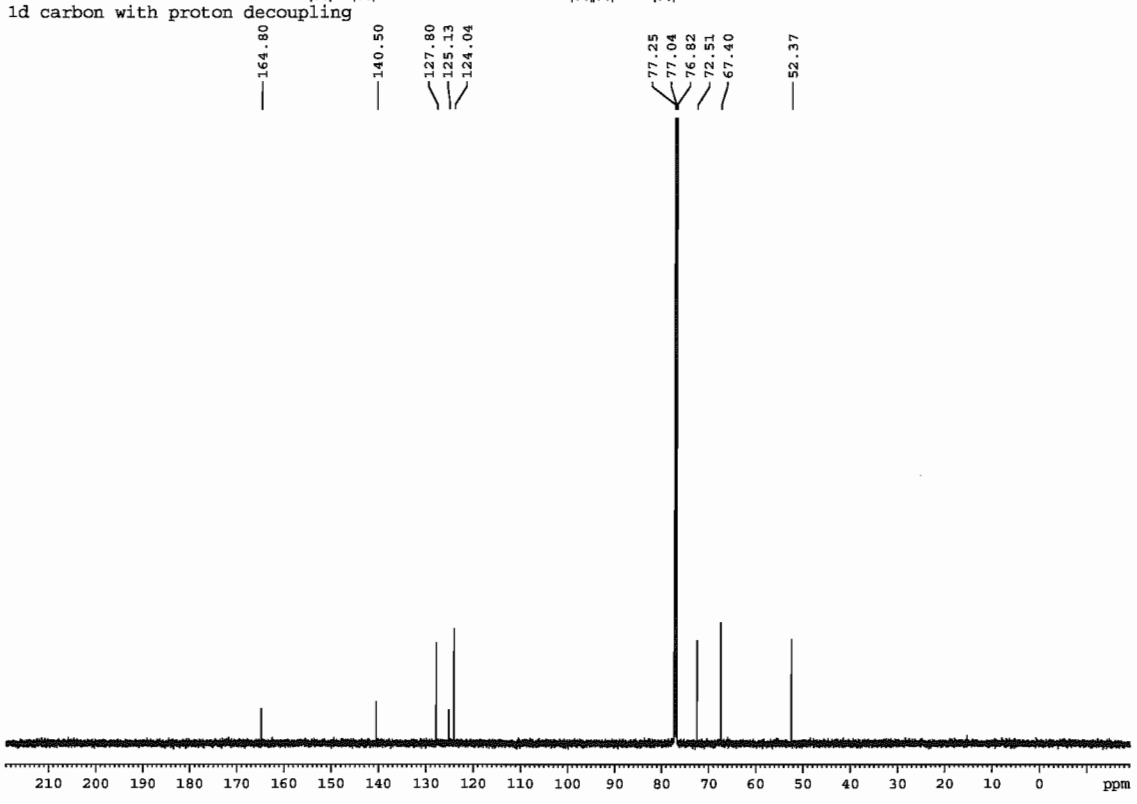
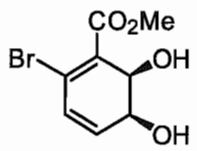
1d carbon with proton decoupling



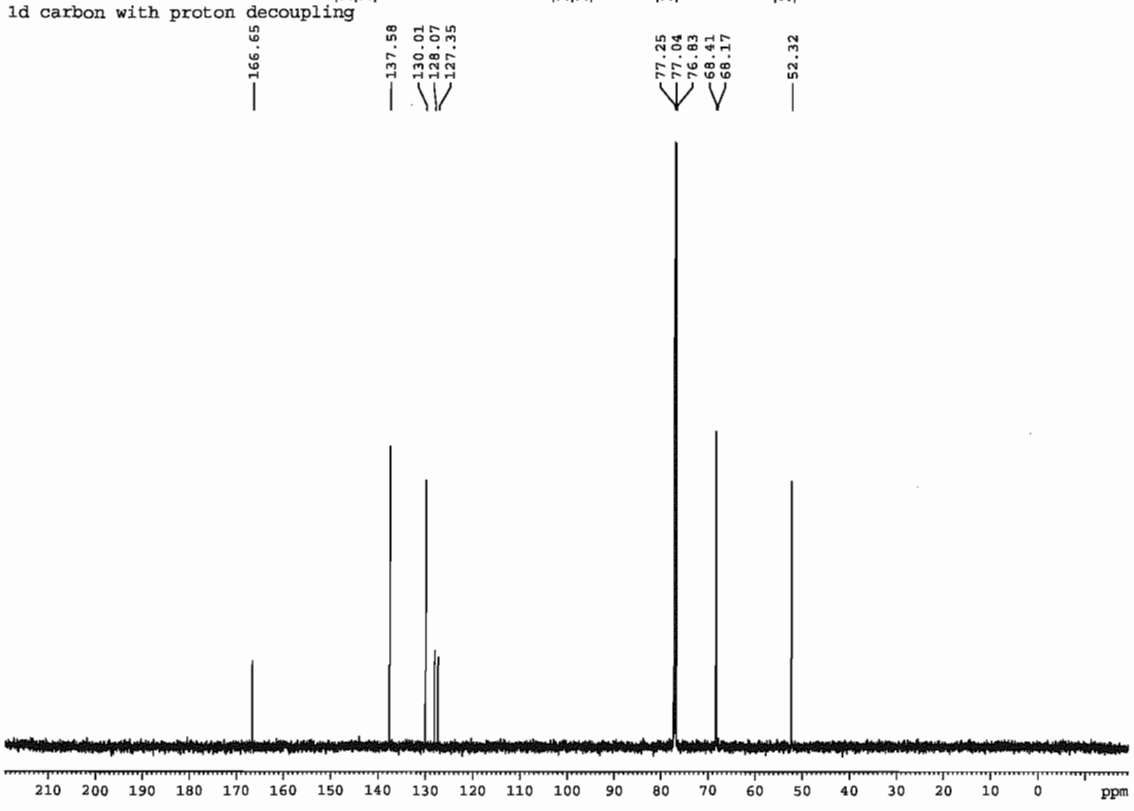
1d proton



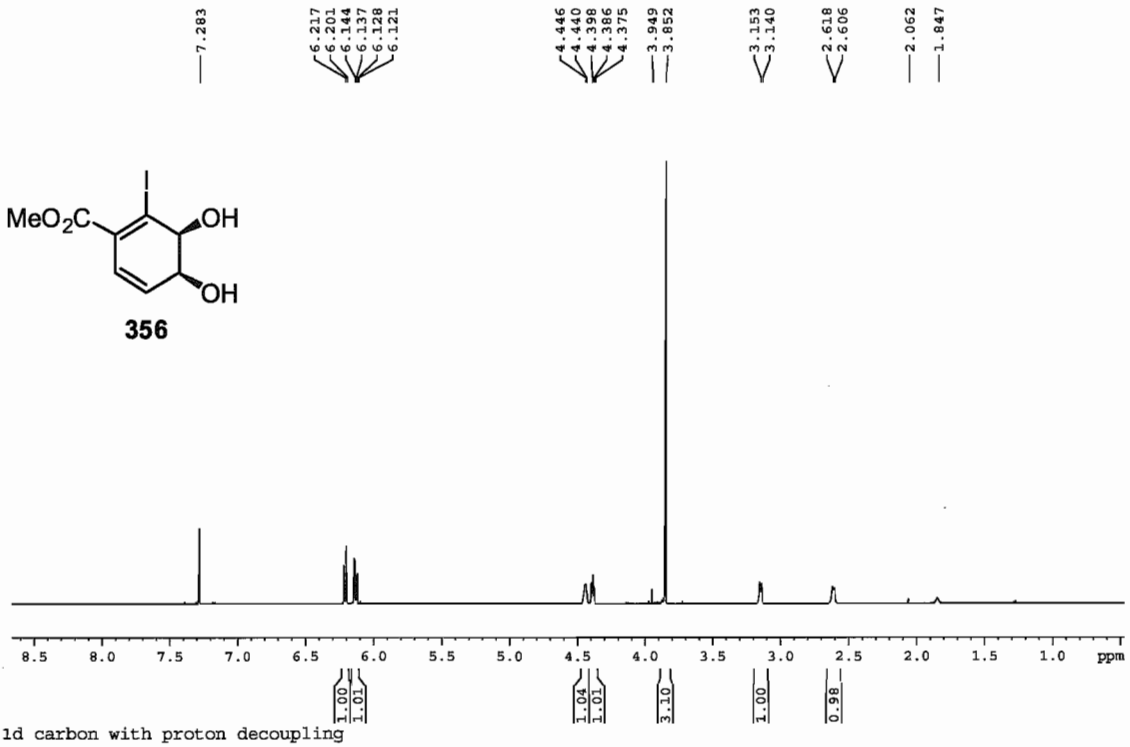

**352**



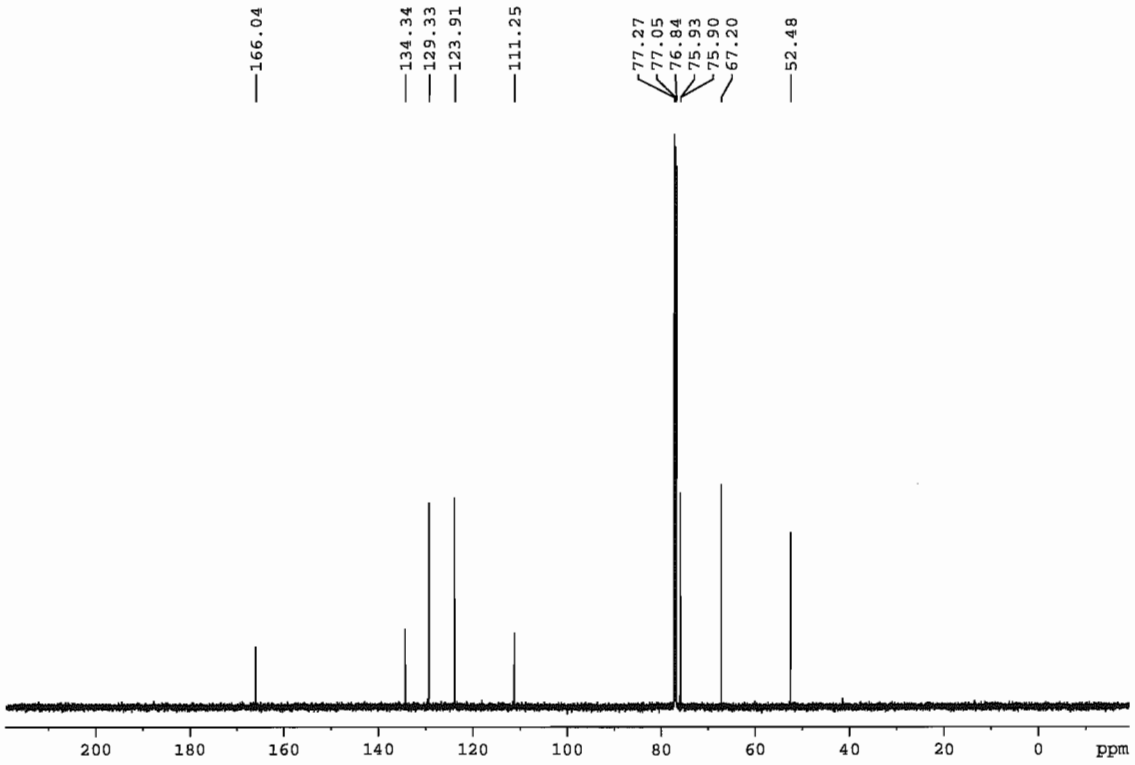

1d carbon with proton decoupling



1d proton




1d carbon with proton decoupling



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## 8 Vita

Thomas A. Metcalf was born in Albion, NY on December 18, 1984. He and his three siblings Lynn, Benjamin, and Anna were raised by their parents, Michael and Kay Metcalf on their family farm. He attended Albion High School and graduated with the second highest GPA in the class of 2003. During his high school years, Thomas was a member of the Albion Cross Country and Albion Track and Field teams. The highlight of his running career was a second place finish in the Western New York steeple chase finals in 2002. Throughout school, he was active in the Boy Scouts of America and attained the rank of Eagle Scout in 2002. After graduation from high school, he attended the University of Guelph in Guelph, Ontario, Canada. He completed a BSc. in Biological Chemistry in 2007. In 2007, he completed an undergraduate thesis under the direction of Dr. Adrian Schwan. Upon completion of his BSc., Thomas moved to Brock University in St. Catharines, Ontario, Canada to pursue graduate studies under the direction of Dr. Tomas Hudlicky. He is presently working towards a Master's degree in Organic Chemistry. His research interests include developing more stable versions of the Burgess reagent and the application of biotransformations in the synthesis of natural products.